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Speaker Profiles

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On completion of the instructorship, Peter returned to Melbourne where he is currently working at the Melbourne Veterinary Specialist Centre. Peter has been involved in undergraduate and post-graduate training in both oncology and internal medicine in both the United States and Australia.

Program

9.00 – 9.45	General introduction to oncology including discussing cancer with clients. Mechanisms of cancer development and progression. Future trends in cancer care.
9.45 – 10.30	Basic principles of oncology including staging, chemotherapy, oncological surgery and radiation therapy.
10.30 – 11.00	Morning Tea
11.00 – 11.45	Canine lymphoma
11.45 – 12.30	Feline lymphoma
12.30 – 1.30	Lunch
1.30 – 2.15	Mast cell tumours
2.15 – 3.00	Soft tissue sarcoma
3.00 – 3.30	Afternoon Tea
3.30 – 4.15	Gastrointestinal tumours
4.15 – 5.00	Paraneoplastic syndromes and palliation of the cancer patient

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NOTES:

General Introduction to Oncology

Peter Bennett
BVSc FACVSc DACVIM

Oncology or cancer management suffers from a number of problems, mainly it is associations and misperceptions about a range of things. The main ones are the term cancer, chemotherapy, radiation therapy, surgery and other terms that all carry a degree of fear for many of our clients.

For many years there was not a lot of attention paid to the treatment and care of small animal patients with cancer. But neoplasia is the most common chronic disease that affects dogs and cats with about 50% of patients dying either due to a neoplasia or who have had a neoplasia in their life. This is similar to people with most estimates being about a 40-45% lifetime risk of neoplasia.

There is a lot that can be done for these patients. Many of these patients can be cured with cancer being the most curable of the chronic diseases. Many can have a long survival as long as there is an early diagnosis and appropriate recommendations are made. Not all clients will be able to pursue the ideal options, but this is the option that should be offered as the first choice. Not all options are available in all areas, but some people are willing to travel to obtain the best outcome.

For many clients and veterinarians the first biggest hurdle is the word cancer. This is thought by many people as being a death sentence. But the number of cases where death is an imminent concern is relatively small. In most cases there is time and options that can lengthen and improve the quality of life for the patient.

WHAT DO I DISCUSS WITH THE OWNERS OF PATIENT WITH CANCER?

This is where the phrase “cancer is a word, not a sentence” has its application. Cancer is a common chronic disease that we see with increasing frequency in our patients. I specifically do not avoid using the word cancer when talking with clients. I do not overly stress it, but by using the term many clients will then realise the

potential severity of their pet's illness and understand why many of the options are being discussed. There are many connotations that abound in the lay and veterinary populations that can make treating cases more difficult.

The most common of these are:

- *“Don't tell me it is cancer”.*

As cancer is the most curable chronic disease, this really does not make sense. This is really a fear based on lack of information and it can be changed, but it requires some effort. I have had patients with patients that might have a tumour or some other medical problem tell me this, and I have replied that if I do find a cancer the outlook is much better than the medical differential. When I first started working in oncology people asked me if this was a depressing area to work in as my patients all die. In reply to this I tell them that more of the patients I see in internal medicine die than in oncology.

- *“If they have chemotherapy they will get sick”.*

This is another common misconception and can be hard to dissuade owners because someone told them about their cousin's friends' dog that got really sick when it had chemotherapy. The usual problem of a study of $n=1$. Or their grandmother was really sick when having chemotherapy. Both of these situations were real, but this is not what happens in the majority of patients. Often, especially with human relatives, it is not clear what is an effect of the medications and what is an effect of the underlying disease.

- *“You can spend a lot of money and they will not get better”.*

By “not getting better” they mean that the patient will not be cured. There are many diseases with this outcome. I have spoken with vets who tell me that they would not consider or recommend chemotherapy to anyone for this reason. But they will treat dogs with severe heart failure, diabetic ketoacidosis or chronic arthritis. I could then ask how many of these they cure. As mentioned previously, cancer is the most curable of the chronic illnesses.

- *“It's awfully expensive”.*

This is true and many people will spend many thousands of dollars on treatment. There are several surveys now where they have asked vets for the major reason why owners will not do a procedure, and the most common reply is that the owners could not afford it or were not willing to pay for it. When they have then approached the owners whose records were reviewed and asked them why they did not go ahead with a procedure,

the most common reply was that they were not told about the option. There are always problems with studies based on recollection by a person. I have had clients ask me the same question about five times over a period of a week and then a week later ask it again and want to know why we did not discuss it before. Memory is not a perfect tool. The clients that I have seen who spend the most money are generally not the very rich, but people who have a close relationship with their pets. As a profession it seems we often presume that our clients are not prepared to spend money or that a client is cannot afford to spend more than a certain amount of money.

WHAT IS A NEOPLASIA?

A neoplasia is an uncontrolled growth of cells. If they remain in one location and grow in an expansile manner they are termed benign. Infiltrative and metastatic behaviour leads to the term malignant. There are many cases where there is not clear distinction between the two groups. There is also overlap of the mechanisms of development. One of the areas of interest to researchers is why some tumours are benign and while other closely related tumours are malignant. If the reason for this difference could be clearly identified then this may help in the development of therapies to reduce or stop invasive or metastatic spread.

WHAT ARE THE CHANGES WITHIN A TUMOUR CELL?

The basic premise is behind the development of a tumour is dysregulation of the normal cell cycle. The normal cell cycle can be thought of in fairly simplistic terms. The first gap phase, G_1 , is where the cell prepares the basics for formation of proteins and is a relatively inactive part of the cycle. The S phase is where proteins, DNA and other materials are being formed prior to cell division. Then there is a second gap (G_2) where there are modified to their final form prior to the cell division itself, the M phase. There is also a resting phase called G_0 where the majority of the cells in the body are present at any one time. The cells enter this period soon after the M phase. At many stages of the cell cycle there are multiple check points where the cell materials are checked for mutations or other disruptions to normality. Some of these are the checks and balances that are lost in neoplastic cells.

But more than the cell cycle is disrupted. Growth of a tissue is a balance between cell division and cell death. Therefore for a tumour to grow there can be either an increase in cell division or a decrease in cell death. The cell death is usually through apoptosis, an active death of the cell that requires energy and is an orderly process rather than necrosis. There are some tumours where increased cell division is the major abnormality. In others it is disruption of the mechanisms of apoptosis. This can lead to differences in response to treatment with chemotherapy and radiation, as both of these methods rely on the induction of apoptosis as a major pathway for causing cell death.

The reason for the alterations can arise from within the cell or from external factors. Within the cell the promoters of the cell cycle can be termed proto-oncogenes because if their control is lost or they become autonomous then they can become oncogenes, or genes that will promote cancer. The negative regulators of the cell cycle are termed tumour suppressor genes. As the name implies they act to stop the formation of the neoplasia and generally are the genes that regulate the checkpoints and apoptosis.

The proto-oncogenes can be activated through a range of processes. The mechanisms were discovered when people were examining the process of viral carcinogenesis. In some cases there is insertion of a promoter (a DNA sequence that up-regulates the expression of the following gene) into the genome prior to a proto-oncogene. In other cases there was insertion of one or more copies of a viral proto-oncogene into the genome. But similar events can occur when there is translocation within a cell, when chromosomal material is moved from one chromosome to another. Mutations from external sources such as ultraviolet light or tobacco smoke. In some cases the gene becomes autonomous and no longer requires a signal for expression of the gene. In other cases there can even be alterations in the signalling pathways and the gene expression can be increased by factors that would not normally cause the response, often another cytokine.

There are also factors outside of a tumour that will alter its chance of growing. The most important of these is blood supply. For a tumour to grow it has to stimulate the development of a blood supply to deliver oxygen and nutrients as these can only diffuse a few millimetres. There is a combination of direct and indirect stimulation of the growth of blood vessels by tumours. These blood vessels within a tumour are often abnormal with a much higher cell turnover and abnormal surface antigens present. This offers alternative means of treating tumours or targeting more conventional treatments to the tumour.

The above is the traditional view of cancer formation. In recent years the complexity of the development has been shown to be much greater. As well as changes in the DNA of the cell there can be changes in the signalling pathways from the cell surface to the nucleus, changes in the transcription and regulation of RNA within the cell, alterations of the proteins in structure and function within the cytoplasm of the cell and even the metabolism of the tumour cell can all be abnormal.

The second major area is the process of metastasis. This is also not a simple process as cells do not drift away from the primary tumour and settling into a distant site. If this was the case then most of the time we should see metastatic lesions in the first capillary bed that they reach, but this is not the case. It has been shown that benign tumour release hundreds or thousands of cells into the circulation every day, but no distant lesions develop. For a cell to develop a metastasis it has to loosen its attachment to the rest of the tumour, migrate through the interstitium to a blood or lymphatic vessel, get through the vessel basement membrane and between the endothelial cells, survive the traumas of travelling in the circulation, avoid the immune system when not in the protected environment of the tumour, attach to the endothelium at a selected distant site, again transverse the endothelial and basement membrane barriers, move through the interstitium, avoid the local immune system, start to grow and then induce the development of new blood vessels. Each of these steps often involves several processes and some are still only partially understood.

HOW DOES A TUMOUR ARISE?

This is a complex process and requires several features in the cells of the body to fail. There are many reasons for mutations to occur in DNA; the best recognised in man being ultraviolet light and cigarette smoke. But there are many others we are all exposed to on a daily basis in the environment and foods that we eat. Internal factors such as inflammation can play a role in neoplastic transformation. But the body has mechanisms to recognise damage to the DNA in cells and if present to stop the cell cycle and allow either the damage to be repaired or the cell to undergo apoptosis or programmed cell death.

In cells destined to become neoplastic we need firstly the damage to occur to the DNA, RNA, cellular proteins or cell metabolism and this has to be in a form that will interfere with the normal control mechanisms of cell growth. We need this to be missed by the survey mechanisms or if recognised for the repair of the defects

to be ineffective but cell death pathways not to be triggered. This usually means we need several defects and in most cases the defects need to arise in a set order. The control pathways are not simple and there are many pathways for all of these areas and so if one is not functioning properly there are backups. Usually more than one pathway needs to become dysfunctional for the neoplastic process to continue.

There are some key factors in the cells and if these are dysfunctional then the chance of a neoplastic transformation occurring is increased. An example of this is the p53 protein. This protein is a regulator of the apoptotic pathway and if a person is born with a defective gene that codes for this protein then there is an increased risk of neoplasia. There are some people born with a defective form of this protein with a markedly increased risk of cancer. But these might not occur until later in life if other events do not occur but their lifetime risk of neoplasia is very high.

In most veterinary cases we do not have an obvious cause for the neoplasia to arise. Epidemiological studies for a variety of cancers has lead to some associations, but often they are not consistent between studies. In people there are some well identified associations such as between smoking and oral or lung cancer; excessive alcohol consumption and pancreatic cancer; and industrial dye exposure and bladder cancer.

HOW DO WE TREAT NEOPLASIA?

The best option is to prevent neoplasia. Preventing cancer is still the most effective treatment as in most cases the prognosis is only fair to poor once the tumour has developed. There is a significant research initiative in these area currently but it is hampered for most human and animal cancers as there is not easily identifiable risk factors, known populations at risk or causes. For a treatment to be effective it needs to be used on those at increased risk and so know who is at increased risk. In people smoking cessation, sensible alcohol use, workplace practices and dietary recommendations are the major methods used to date. There is little information in the veterinary fields about preventative measures being used successfully.

The standard treatments are surgery, chemotherapy and radiation used either alone or in combination. There are some novel treatments being developed in people but many of these are not available or they are cost prohibitive for our patients. There is a further option and this is palliation and this is one area where we can often do a lot more than is currently being offered to our

clients either as a single treatment or in combination with the conventional therapies.

To decide on what is the best treatment relies on us knowing what disease process is present. If we do not have this information we do not know what the options will be best, what the prognosis will be and more importantly what other steps are recommended prior to definitive therapy. The most important first step is usually a biopsy of a lesion to obtain this answer.

FUTURE TRENDS IN CANCER TREATMENTS

Currently the standard of therapy is to get a histological diagnosis and base treatment recommendations on this report. With the increased knowledge of the molecular biology of cancers this may be used less often. There are tumours that are from very different cells of origin and so have very different histological appearances that share common defects. In the dog both mast cell tumours, a round cell, and gastrointestinal stromal tumours, a sarcoma, both have mutations in the c-kit gene. There are now drugs that can target this mutation and so the same treatment may have benefit in two quite diverse tumours.

The thought is that in the future there will be extensive testing of the mutations and other changes within tumour cells and this will guide the treatment or treatments used. There is still a huge amount of work needed to identify the major defects and how to best treat these when they occur alone or in combination. Screening for multiple defects is becoming easier with newer technologies such as gene chips that can look at the expression of thousands of genes in a very small sample of tumour. Currently these are fairly expensive and each species would require their own versions. But the improved outcomes and possible cost savings in knowing that the treatment is the best option for that patient may well outweigh this problem. This is the first step in truly individualised treatment planning.

A further step in this pathway is the development of sensitive markers for cancer cells. It would may be possible in the future to get a blood sample and know if the patient you are treating has microscopic amounts of metastatic disease present. This will allow good selection criteria of which patients should have adjunctive treatments and also may offer very sensitive monitoring of treatments.

With the development of some of the newer drugs that are not cytotoxic, but alter the metabolism of tumour cells, there is also a

push to develop tests to look at the metabolism of the tumour cells in the patient. Many of these are PET scan based. With many of these drugs there will not be a measurable tumour response or the measurable response can be delayed. An early test to see if the drug is working in an individual patient will be useful.

NOTES:

NOTES:

Basic Principles of Oncology

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The main principles of oncology can be summarised as we need to know what we are treating and we need to know where the disease is located. Both of these are the major determinants in what treatment is appropriate and what the prognosis will be. When we do not have this information, wrong decisions can be made.

In most cases the only way confirming the diagnosis of a mass is through a biopsy for histopathological examination. There are a few exceptions to this, mainly round cell tumours, for clinical purposes, but in all cases the only recognised gold standard is histopathology.

Cytology is a very useful tool and can give some very good information. But there are limitations. The pathologists can only see individual cells and their morphology and not the architecture of the mass and the interaction with the surrounding normal tissues. Its diagnostic accuracy is at its highest with round cell tumours where the cell type is often easily recognised. But even in these cases there are problems. For example a diagnosis of mast cell tumour can usually be made with a cytological evaluation, but the histological grade cannot be predicted. There are some cases where cell morphology and architecture are not sufficient to confirm a diagnosis and special stains or immunohistochemistry may be needed to obtain the answer. In most cases these stains are more readily performed on a histologic sample but there are some cytochemical stains used, but currently few are on offer in Australia.

With cytology there is a greater chance of error. The cell morphology can be influenced by factors such as inflammation. There is reasonable overlap between the dysplasia seen as a result of inflammation and the changes seen in neoplastic cells. Epithelial cells and fibroblasts are the most often cell types where this occurs.

As with all tests the pathology report is not the absolute. The pathologists can only tell you what they see down the microscope. They are not looking at the patient and do not have all the clinical

information other than the brief notes on the request form. Therefore if the pathological diagnosis does not fit with the clinical picture then it is your right to question the pathologist or seek a second opinion. But there times when the pathology and clinical diagnoses do not mesh. These cases are difficult and often can only be resolved with the collection of more samples. Also a cytological diagnosis can include terms such as “suspect” or “consistent with” rather than clearly being diagnostic. But in these cases this report when combined with the clinical picture may be diagnostic.

BIOPSY OPTIONS

There are several options including fine needle aspiration, core needle biopsy, incisional surgical biopsy and excisional biopsy. There are advantages and disadvantages of each of these options as outlined in the following table. There are times where the ideal approach cannot be taken. As long as all involved are aware of the compromises and the potential downsides then you can proceed. It is only when these options are not discussed in full that problems can arise.

Procedure	Advantages	Disadvantages
Fine needle aspirate	☐ Easy and fast to do ☐ May not need even sedation ☐ Fast results ☐ High positive predictive value in most cases ☐ Cheap	☐ Can be misleading ☐ Cell type and not tissue architecture examined ☐ Low negative predictive value ☐ Some cells types do not exfoliate well
Core needle biopsy	☐ Can be done with local and sedation ☐ Easy to do ☐ Relatively inexpensive ☐ Histopathology done	☐ Small sample size ☐ Subject to artefact ☐ Boundary between mass and normal tissues not examined ☐ Centre of mass may be necrotic
Incisional biopsy	☐ Large sample for pathologists ☐ Histopathology done ☐ Boundary can be included	☐ Generally needs anaesthesia ☐ Expensive
Excisional biopsy	☐ Best sample for pathologists ☐ Histopathology done ☐ Margins included ☐ May be curative	☐ Don't know what margins to take ☐ Needs anaesthesia ☐ Expensive

CELL TYPE VERSUS TISSUE ARCHITECTURE

There are some situations where normal tissues can have a population of cells that look malignant if seen in isolation. The classic examples of these are reactive fibroplasia and mesothelial cells. In both of these situations the cells can have many of the characteristics of neoplasia, but they are not neoplastic, they are reacting to inflammatory factors in the local environment that cause changes that mimic neoplasia. In these cases the architecture of the tissue will enable a determination of whether the cells are benign or malignant, but even then there are times when this is not possible. The sample size given to the pathologists can be very important.

There are some situations where malignant cells can look normal. This is most often seen in cases such as small cell lymphoma and thyroid carcinoma. In these cases the architecture of the tissue is

needed to show that we are dealing with a malignant process rather than a benign one. At times the only way a malignant process can be identified is at the interface between the lesion and the surrounding normal tissues. This is why a peripheral biopsy of a lesion may be of more value than a biopsy from the centre, but there are exceptions. Also the centre is often an area where necrosis is found.

COST

We can get caught chasing false economies. The owners of some of our pets want the cheapest options. We have to discuss the implications of cutting costs. We have all seen the client who presents a dog with a lump, and wants only for the lump to be removed with no preliminary work or histopathology. This will often lead to problems. If you are going to remove the lump, what margins are you going to take? The margins can be less than 1 cm for a relatively benign mass such as a lipoma, to more than 5 cm for a haemangiopericytoma and both of these masses can appear identical on palpation. There are some cases where preoperative biopsies will not alter the initial therapy. If there is a mass that is causing the dog problems because it is bleeding and it is in an area where it is simple to get wide margins such as the flank, then an excisional biopsy would save money, and no matter what the diagnosis the surgery most likely will still be done. In the former situation doing 5 cm margins for a lipoma is needless, and marginal excision of a haemangiopericytoma will lead to recurrence and the need for more extensive surgery. It is harder to do surgery in an area where surgery has previously been performed as the margins have to be from the previous surgery site, not the mass, and so second surgeries always cost more than a primary surgery. We should try to avoid the statement ‘I wish I knew that before I did the surgery’, as in most cases if we take the appropriate steps, we can know ‘that’ prior to doing the surgery.

STAGING

Staging is the process of examining the patient for distant disease and evaluating the extent of local disease. It is never wrong to fully stage a patient with a malignant or suspect malignant disease. There are some cases where staging will not alter the recommended treatment, but still might alter the prognosis or the subsequent testing that was done on that patient.

WHEN TO STAGE

When we have a disease that is known or thought to be malignant then staging is appropriate. The more involved the treatment, especially if it is a purely local treatment such as surgery or radiation, then the more imperative is the staging. In many cases staging is done prior to obtaining a diagnosis. This is when there is a high chance that the mass is malignant based on clinical or sometimes cytological findings. An example of these would be in a dog with an ulcerated mass arising from the hard palate in the mouth. This is usually going to be a malignant tumour.

As a by-product of staging evidence of concurrent disease that might influence the prognosis and treatment options may be found. As many cancer patients are older there is a higher chance of cardiothoracic, renal and liver disease to name a few.

WHERE TO STAGE

There are several parts of staging. There is local staging to determine the extent of localised disease. There is distant staging in places where disease is known to spread. Finally there are special tests for specific tumours to find other evidence of disease.

Local Staging

This is to look for evidence of the extent of local disease. Visual examination and palpation are the main tests used but these can be inaccurate. In some cases radiographs, ultrasonography and advanced imaging can be of use and in some cases are mandatory. These tests are performed to allow planning of the surgery or other local therapy such as radiation.

Distant Staging

This is typically examination of the regional lymph nodes, the thorax and the abdomen. Palpation of the regional lymph nodes is not sufficient to rule out disease and aspirates or biopsies of nodes that palpate as normal can reveal disease. For the thorax, thoracic radiographs are generally used and ideally three views should be taken. If only two views are to be taken then the opposing lateral views are the ones that will be of most value. Thoracic CT will identify smaller lesions and allows better evaluation of the hilar

lymph nodes, but this requires general anaesthesia. For the abdomen, ultrasonographic evaluation is the most commonly used tool. There are many times when there are lesions seen on ultrasound that are not seen on radiographs of the abdomen. Abdominal CT can be performed but again it requires anaesthesia and does not readily allow sampling from abnormalities seen.

Other Examinations

There are numerous other tests that can be indicated depending on the diagnosis. For lymphoid and other round cell tumours a bone marrow aspirate might be recommended. For bone tumours a nuclear scintigraphy of the other bones is the most sensitive test for other bone lesions.

BASICS OF SURGICAL ONCOLOGY

This remains, and will probably always remain, the most effective means of treatment of a tumour.

General Concepts

Many oncological surgeons talk about a surgical dose. This concept brings into mind the effects of altering the dose of other forms of medication. Reducing the dose can lead to tumour tissue being left behind, and recurrence. We know that for many tumours this is associated with a worsening of prognosis. An excessive dose of surgery is associated with no additional benefit to the patient and there can be an increased morbidity or mortality associated with the surgery.

So what dose of surgery is indicated in a particular case. We need to know what the tumour is and where it is. The former is the information obtained from the biopsy while the latter is the result of staging, including careful evaluation of the local disease. There are some cases where more advanced imaging such as MR or CT scans are preferable or even crucial.

What are the aims of Oncological Surgery?

1. The primary aim should be to cure the patient. Surgery will cure more patients of cancer if performed properly than any other form of therapy. To know if this is possible, we need to know what tumour we are dealing with in order to be able to decide whether surgical cure is even possible. We know that for a haemangiopericytoma we can cure most cases if we can remove all of the local disease, while with an osteosarcoma nearly all patients will have distant disease at the time of diagnosis.
2. The next aim is to cure the patient of local disease with the knowledge that there is likely to be distant disease present that will be controlled by other methods, usually chemotherapy.
3. Another aim can be to get a diagnosis. A surgical biopsy is sometimes the most appropriate means of obtaining a diagnosis. What type of surgical biopsy is collected will vary depending on the location of the tumour, clinical suspicion of tumour type and the influence that the tumour type will have on definitive therapy.
4. The final aim is palliation. At times the primary disease is causing the patient distress or pain and surgical removal, while not curative, can be used to palliate the clinical signs. An example of this would be removal of an osteosarcoma.
5. Debulking the tumour means not even reducing the mass to microscopic disease. This is something that is often performed, but is usually not indicated and is often contraindicated. At times when marginal surgery is to be combined with adjuvant therapies in order to increase the efficacy of the adjuvant therapy. There is almost never a role for debulking a tumour if no other therapy is to be used.

Problems Encountered in Oncological Surgery

1. Surgical Morbidity

As cancers occur more commonly in the older patient, their age and potentially other illnesses need to be considered. A thorough physical examination and screening blood and urine tests will reduce the incidence of unexpected problems. Knowing that a patient's renal function is not normal does not preclude surgery, but it does mean that special precautions need to be taken such as fluid therapy prior to, during and after the surgery, avoidance of

hypotensive agents as much as possible and avoidance of the use of non-steroidal antiinflammatory agents. Also in cases where there will be a significant recovery period, care must be taken that this is included in the preoperative plan.

2. Dirty Margins

As mentioned in the previous section preventable causes of this arise usually as a result of one of two situations. The first is surgical treatment of a disease when a diagnosis has not been made prior to treatment and so inadequate margins were taken. The second arises from concerns about trying to close the wounds after surgery. These can be avoided by careful planning, getting a biopsy and considering referral.

3. Spread of Tumour Cells

This is a potential problem that while often a big concern for the owner, in reality the risk is not high. It is a problem that can occur if care is not taken in the planning and execution of the operation. The biggest problem is contamination of the surrounding normal tissues. The aim during surgery should be not to see the tumour itself but a layer of normal tissue over the mass. Seeding tumour into the surgical site is possible with the highest risk being for uroepithelial tumours. But it can occur with any tumour. In most cases surgery will not disseminate tumour widely in the body through the vasculature.

Dissection around the tumour should be kept to a minimum. In cases where sliding grafts, skin flaps or other means of closure are required, then these should be prepared prior to removal of the tumour. This will decrease the risk that tumour cells will be spread into the donor bed and so increase the area that might need subsequent therapy such as radiation or further surgery.

4. The Regional Lymph Node

The problem with the local lymph node lack of knowledge. Should this be removed at the same time as the primary surgery? Should the lymph node be left in place? There are arguments for both sides. The primary argument for removing the local lymph node is that there is a chance that the tumour may have spread to the node and not gone any further. Removal has a chance of decreasing the risk of leaving tumour behind. The second view is that the regional lymph node has an important role in the development of tumour immunity and that this might be a centre for development of a defence against metastatic cells.

5. The Biopsy

Biopsies can cause problems for surgeons. It is possible, as mentioned previously, to seed the tissues surrounding a tumour with cells during surgery, but it is also possible to do this during a biopsy procedure. This is not restricted to surgical biopsies but can also be seen with ultrasound guided and other needle biopsies. The risk with a fine needle aspirate is much smaller. There are very few reported cases of tumour seeding occurring in the veterinary or human literature in association with fine needle aspiration, but there are numerous with biopsy needles. Seeding of the body wall is seen with uroepithelial tumours and also respiratory tract tumours.

The site of a biopsy and the tract from the biopsy entry to the tumour should all be considered contaminated and the plan should be that all of this tissue is removed as a single unit along with the tumour at the time of definitive therapy. Therefore some people recommend that biopsy is collected by the person who will be performing the surgery, or at least in consultation with that person.

We can learn a lot from biopsies, but some care does need to be taken when planning the approach. It has been seen in human oncology that a significant number of patients (as high as 30%) require more extensive surgery (amputation versus limb salvage) due to poorly placed biopsy.

Alterations in Wound Healing in Oncological Surgery

There are several factors that need to be covered here. We have the alterations in metabolism that occur in cancer patients and these can lead to reduction in wound healing. If cancer cachexia is present then this will significantly slow healing. If there is neutropenia or anaemia then these will affect healing by increasing the risk of infection in the former case and decreasing oxygen and nutrients in the latter. Hypoproteinaemia can significantly reduce wound healing.

There are varying suggestions as to problems with tumour left at the surgery site and its effects on healing. Some say that wounds with lots of tumour do not heal as well as normal tissues, while others report that there is no real difference. This is an effect of the type of tumour more than the amount of tumour. Mast cell tumour is one type that does have a significant impact on wound healing. The lymphoid tumours can also cause problems and I have seen wound dehiscence in a number of patients with intestinal lymphoma.

Radiation and chemotherapy also alter wound healing. In most cases radiation can be done prior to surgery or once the initial phases of repair have occurred, especially revascularisation of the area. The effects in most cases are not significant if allowance is made at the time of surgery. It is also important to note that metallic implants can affect some forms of radiation, especially orthovoltage treatments. There is much less impact with the now more commonly used megavoltage treatments. Chemotherapy agents also have impact, but it is not usually clinically significant. It has been my experience that glucocorticoids have had more influence on wound healing than any of the other drugs that we regularly use.

THE BASICS OF CHEMOTHERAPY

Chemotherapy are the only commonly used therapy that treats the whole patient. They are classically used to treat systemic neoplasia or metastatic disease. There can be a role as treatment for local disease in some situations. Chemotherapy is the least likely to affect a cure of the three major options for treating cancer.

The most common misconceptions about chemotherapy are that all patients get sick when the drugs are used and secondly the complete remission is the same as cure. Both of these are wrong. The majority of patients who are treated with chemotherapy have minimal toxicity, if any. There are some patients who do experience toxicities, which have the potential in rare cases to be life threatening, but these are the exceptions rather than the rule. I quote to owners that 70 – 80% of patients have minimal toxicity.

The concept of remission is a problem for some owners, as no matter what they are told, will see the lesions disappear and then are disappointed when they recur later in the course of the disease. I have seen this most often with lymphoma where there is generally a complete remission, but rarely a cure.

HOW DO WE USE CHEMOTHERAPEUTICS?

There are several principles that need to be followed. These are:

1. We must have a diagnosis with histopathology the minimum in most cases.
2. We should know where the disease is located and the amount of disease present.

3. We must know the general health status of the patient.
4. We should use the most effective drug or combination of drugs that has been shown to be effective for the disease.
5. The treatment must be given safely with consideration to the patient, staff and owners.

We will cover each of these points in more detail.

Diagnosis

This might sound obvious, but there is always the temptation to treat because we think that we know the diagnosis. This can lead to problems and if we do not know what we are treating we cannot choose the best treatment, we cannot give a prognosis, we cannot know where to look for additional disease and for potential adverse reactions. There are a few situations where treatments are given without a confirmed diagnosis which include brain tumours and right atrial tumours. In these cases there is often a good information from imaging and other tests.

Where the Disease is Located

Again if we do not know where the disease is located then it is difficult to assess if we have a response. We cannot presume that all the disease present in a patient will respond in a uniform manner.

General Health Status

The general health of the patient can influence treatment in a number of ways. The most important organs are the liver and kidneys as these must be functioning normally for the chemotherapeutic agents to have a normal metabolism. If it is altered and the usual dosage schedule is used, the risk of toxicity (or occasionally lack of efficacy) is increased.

Choice of Drug or Combination

This is an area that the veterinary profession often finds itself deficient. Ideally for any disease treated we should have the results from a number of trials that have shown a drug or combination give overall the best results. There are a few diseases that come close to this ideal including TVT, lymphoma, haemangiosarcoma and osteosarcoma. But even for these the range of treatments that have been trialled are limited and most of the original choices were extrapolated from the protocols used in man. It is not always

possible to extrapolate from one species to another and we cannot even reliably do this between the dog and the cat. There are many diseases that we treat based on small studies, sometimes reports of responses in less than twenty dogs. This is a long way from the studies in human oncology where hundreds, or in some cases thousands, of patients are enrolled.

Drug combinations cause even more problems as the interaction between drugs will alter if their pharmacology differs and this happens between species. Ideally all the drugs used in a combination should have been shown to have activity as a single agent. Recent work has now shown that there are some (possibly many) drugs that while they do not work as a single agent are synergistic in combination. Use of combinations generally increases the responses seen and with careful selection there can be a decrease in the toxicities seen at the same time.

Safety

This is a major area of concern. Chemotherapy drugs are similar in this respect to radiation in that most appear as harmless liquids or tablets. The effects of exposure might not show up for years or decades. Therefore it is easy to be complacent about their use. There are legal requirements in many areas and a full outline of the Victorian legislation is outlined on the Worksafe website at www.worksafe.vic.gov.au.

What do you need in the clinic?

There are a number of things that are important in the administration of chemotherapy agents. While not all of these are strictly necessary the more that are in place, then the safer the environment will be.

1. A dedicated room for the storage, preparation and administration of chemotherapy agents. This would be ideal, but while we do have this in our centre, it is not practical in a general practice.
2. A secluded and quiet place to administer the drugs where there will be no through traffic during the course of the administration.
3. A spill kit.
4. Disposal containers.
5. Protective clothing.

6. Appropriate storage and preparation areas for the drugs.

Chemotherapy Agent Storage and Handling

Secure storage in clearly identified containers is required. As many agents need to be refrigerated this means in a spill proof container in a fridge (we have a dedicated fridge) that is not used for food or drink storage. Drugs that are stable at room temperature should be kept separate area of the pharmacy and the area clearly labelled as having cytotoxic drugs present.

If possible in-house preparation of drugs should be avoided where possible, and as mentioned previously it is illegal in some areas. There can be some cost saving, but it is minimal if the time, materials and potential exposure of staff is considered. Pre-prepared syringes from a commercial supplier are the means of choice. If drugs do need to be prepared on site then the ideal situation is to have a cytotoxic rated fume hood in which to prepare the drugs. An alternative are closed systems such as the Phaseal system.

Owner Safety

The owners also need to be warned about the potential risk of the use of these agents. Their pet will be excreting some drugs in the urine, faeces or saliva and they need to be made aware of this prior to starting chemotherapy. We do not need to cause hysteria, but they, like the staff, need to be informed. I discuss similar things with the owner as I do with staff members.

I warn the owners that there is a potential risk if they are exposed to the drugs. I warn them that the risk is higher for pregnant women and the young. The major risk to the owners comes from urine, faeces and saliva that may contain active drug or metabolites. I usually describe what the owners need to do as rigorous implementation of the normal hygiene recommendations. This means wear gloves if urine or faeces need to be cleaned and if possible do not clean up faecal material from outside. Exposure to the environment, particularly ultraviolet light, will break down most drugs relatively quickly. Care must be taken if there is an accident inside or when cleaning cats' litter trays. I usually warn the owners that the risk is greatest in the 48 hours after drugs have been administered. This is given to them in writing prior to chemotherapy starting. Avoidance of procedures that could cause aerosol formation must be avoided.

Care must also be taken with drugs that are dispensed to be given by the owners. We use containers with child-proof lids, label with a cytotoxic label, supply them with gloves for administration and allow them to return these items for disposal in the cytotoxic waste. Children and pregnant women should not handle the drugs at all. Tablets should not be split as this exposes the owners to the drugs. Also some tablets such as cyclophosphamide do not have uniform distribution of the drug throughout the tablet.

Patient Safety

The main issues for the patient are that we need to know the disease that we are treating and the drugs that we are using. Complex combinations of drugs have more potential interaction than simple ones and this information is also needed.

Safe administration of the drug is important and the person administering the drug must be familiar with its manner of administration as well as acute (during administration) toxicities that need to be monitored. The most common problem seen is extravasation that for some drugs can have minimal effects, while in others the effects can be catastrophic.

HOW DOES CHEMOTHERAPY WORK?

Each class of chemotherapy drugs acts in a differing manner. Overall the summary is that the agents interfere with DNA either by damaging nucleotides, causing insertion of non-functional nucleotides, formation of cross-link between the DNA strands or interfering with other aspects of DNA transcription or repair. The end result can be failure of DNA replication, failure of RNA synthesis, formation of nonsense readings or often a combination of the above. Cells have a number of pathways that look for DNA damage. These are why we all do not die of tumours at a very young age. These pathways are preserved at least to some degree in tumours and when damaged DNA is detected the cell cycle is arrested. This allows for repair of the damage or when this is not possible the apoptotic pathways are activated leading to the death of the cell. Most tumour cells are not as efficient in repairing DNA damage as normal cells and it is this selective advantage that we use to kill the cancer cells but not the host. Some are damaged, most commonly in the gastrointestinal epithelium and bone marrow, leading to the most common toxicities that we see.

WHAT ARE THE MAJOR CLASSES OF DRUGS?

The Antimetabolites

These are a group of drugs that consist of modified nucleotides or substrates for vital enzymatic reactions within the cell. By changes in structure they alter the function or inactivate enzyme systems. Most are relatively specific for the S phase of the cell cycle. The more commonly used members of this group include methotrexate, cytosine arabinoside, 5-fluorouracil, azathioprine, hydroxyurea and gemcitabine.

The Vinca Alkaloids and Other Antimicrotubule Agents

While microtubules are commonly thought of as being important during mitosis and their role in separating the sets of chromosomes, they also play a roles in maintaining cell shape and scaffolding, intracellular transport, secretion, neurotransmission and possibly in the transferral of signals from the cell surface to the nucleus. The more commonly used drugs in this group are vincristine and vinblastine.

Alkylating Agents

This group of drugs had an important role in the development of anticancer drugs. They were the first non-hormonal agents to be shown to have anticancer activity in humans. There are two types of reaction that can occur. The first is where a highly reactive intermediate is formed and this then reacts immediately with a nucleophile to produce the alkylating product. In the second type the alkylating reaction is dependent on the concentration of both the alkylating agent and the target nucleophile. There are some drugs that have a combination of both types of reaction. The commonly used drugs in this group include cyclophosphamide, chlorambucil, CCNU and dacarbazine.

Platinum Agents

Once within the cell there are displacement reactions and this then allows the platinum to become stably bound to DNA, RNA, proteins and other molecules leading to a wide range of disruption to both nuclear and cytoplasmic function. This accounts for their wide range of activity. When platinum agents bind to DNA they

will attach to two sites on the same strand leading to a DNA adduct or to different strands leading to cross linkage. Cytotoxicity is via induction of the apoptotic pathways. Cisplatin and carboplatin are the drugs commonly used in veterinary medicine.

The Antitumour Antibiotics

Some antibiotics when being evaluated for antibacterial activity have also been shown to have activity against eukaryotic cells. These act generally by binding to DNA and inhibiting RNA and protein synthesis. Actinomycin-D is the most commonly used of these drugs.

Anthracyclines and Anthracenediones

This group of drugs, particularly doxorubicin, are among the most widely used antitumour agents. They are really a subset of the antitumour antibiotics. They have a wide range of activity and also do not have any antagonistic effects with any of the other antitumour agents used. Their mechanism of action is varied with inhibition of topoisomerase, binding to DNA and formation of reactive oxygen species. Doxorubicin, epirubicin and mitoxantrone are the main drugs used.

Miscellaneous Agents

This includes drugs such as L-asparaginase which breaks down the essential amino acid L-asparagine which some tumour cells (mainly lymphoproliferative tumours) cannot synthesize. Bleomycin which is a complex drug that has a combination of peptides that cause direct DNA damage. Finally glucocorticoids are listed here as they can lead to lysis of lymphocytes, particularly malignant ones, through as yet unknown mechanisms.

RADIATION THERAPY

Radiation therapy has a relatively short history of use in veterinary oncology. Its use is increasing and more and more information is being developed about its use. The main problem is that outside North America there is limited availability for veterinary patients. Dedicated veterinary units are really needed as the limited access

that is available to human units precludes the use of the standard three or five day a week protocols.

Radiation is useful in treating local disease, similar to surgery, but there are a few cases where whole or half body therapy can be used with some benefit for systemic disease such as lymphoma. The treatment of local disease can be curative or palliative.

The main form of radiation used is teletherapy where a beam of radiation from an external source is used. Other forms include systemic therapy (for example ^{131}I for thyroid tumours) and brachytherapy where radioactive sources are implanted directly into the tumour.

RADIATION PHYSICS

There are two units used in radiation biology. The first is the unit of exposure, the roentgen (R), which is used in the output of units such as X-ray machines. The unit of radiation absorption, the gray (Gy), is the unit that is used in describing the dose that a tumour is given. This is the biologically important unit. The difference between the delivered amount of radiation, measured in roentgens, and the absorbed dose, measured in Gy, is a quality factor that is dependent on the tissue and the amount of radiation that tissue will absorb.

When radiation strikes a tissue, there are a number of possible events. The first is the photoelectric effect, which is seen with lower energy beams such as diagnostic radiography. In this an electron is ejected from an inner ring and an outer ring electron fills the space emitting a characteristic X-ray. The Compton Effect, which is the main effect in therapeutic radiation, is where the photon interacts with an outer shell electron and transfers some energy to it. The electron recoils or is ejected, leading to ionisation. The higher the energy of the photon, the higher the percentage of energy transferred to the electron. The final effect is where the photon interacts with the nucleus and produces pairs of annihilation photons.

The final general concept is Linear Energy Transfer (LET). This is the deposition of energy along the tissue path. This increases with the size of the particle and its charge and decreases with the velocity of the particle. Therefore a large charged particle moving at slow speed will deposit more energy over a shorter distance and so have a more superficial or local effect. This has a role in brachytherapy.

RADIATION BIOLOGY

Radiation has an effect in several ways. There is a direct killing of tumour cells via damage to DNA and cell membranes and this is thought to account for less than 30% of cell death in therapeutic radiation therapy. More common is indirect cell killing through interaction of an intermediary molecule, most commonly water, and the formation of free radicals or other active moieties. Cell death can be direct, though this does not happen often except in the case of some very sensitive cells such as lymphocytes. Reproductive death is more common and this is where the cells are no longer able to divide, they die or arrest when they try to divide, or their daughter cells die when they try to divide.

The radiation responsiveness of a cell will depend on a number of factors. The factors that play a role are the reproductive rate, maturity and differentiation, metabolic rate and finally whether they are stem cells. Cells with high mitotic rates, immature or stem cells and those with a high metabolic rate would be the most sensitive. Mature cell populations with low mitotic and metabolic rates would be the least responsive.

Factors that modify cell sensitivity include oxygenation, location within the cell cycle and ability to repair sublethal damage. Oxygenation is the most important factor with hypoxia having significant negative influence on radiation responsiveness.

There are four factors that have a big role in radiation therapy and they are known as the four Rs. They are:

1. Reoxygenation
2. Redistribution
3. Repair of sublethal damage
4. Regeneration/repopulation.

Reoxygenation occurs with a decrease in tumour size but no alteration in blood vessels. There is also a loss of well oxygenated cells closer to blood vessels. Overall there is improved oxygenation of the remaining cells and so an increase in sensitivity.

There will also be a synchronisation of the cell cycle within the tumour. This is due to depletion of cells within the sensitive parts of the cell cycle and is the basis for some of the decisions on fractionating therapy.

Repair of sublethal damage is different in acute and late responding tissues. Acute responding tissues have less capacity for repair than

late responding tissues. In the late responding tissue there is an accumulation of sublethal damage and it is this effect rather than direct cell killing that makes these tissues late responding.

Repopulation of the tumour is from division of cells. The longer the time the more there is a chance of repopulation by tumour cells. Also the faster a tumour is growing the shorter the time course for therapy that should be attempted.

CAUSES OF TREATMENT FAILURE

Basically the most common causes of treatment failure is too low a dose and not including all the tumour tissues within the treatment field. There are no tumours that theoretically cannot be cured by radiation. The problem is the normal tissues surrounding the tumour and the effect the radiation will have on them. In most cases it is the normal tissues that determine whether we can cure a tumour with radiation.

The size of a tumour is important. As cell death within a tumour is a random event and a fixed proportion of cells are killed with each fraction, the more cells that need to be killed to ensure tumour cure, the lower the chances of cure.

Hypoxia is the next problem and it is frequently present. As most tumours are relatively hypoxic or have areas within them that are hypoxic, then this will decrease the sensitivity. The percentage of the tumour that is hypoxic will depend on the size of the tumour, the tumour type, where it is growing and other physiological factors such as the presence of anaemia. Large rapidly growing tumours are at highest risk. The presence of large areas of necrosis on the biopsies is the most common warning sign that we see.

Repopulation during therapy is something that needs to be avoided. The longer the course, the more time there is for tumour cells to grow and replace those killed by the radiation. This is a problem with rapidly growing tumours. Also in some cases there is accelerated regrowth after treatment. This is the reason why multiple fractions are usually used on a daily basis. This allows the largest amount of radiation to be given in the shortest period of time.

Intrinsic radiation resistance is probably dependent on the ability of cells to repair sublethal damage. This is not an absolute reason for failure but in some tumours the ability to repair comes close to matching the normal tissues and therapeutic treatment is more difficult as the therapeutic index is so low. Fraction size of the

radiation increases this problem in some cases. One tumour where this is thought to be important is oral melanoma in dogs, in which a lower number of higher doses per fraction increases the response rate. This is contrary to what usually happens.

There can be reseeding of a treated area by tumour at another location or in the surrounding tissues. Induction of a new tumour has been reported but is an uncommon to rare event.

COMBINING RADIATION AND SURGERY

This has a role in several situations. The first is if there is a low cure rate with either surgery or radiation when used as a sole therapy. The next is in tumours with a high rate of local recurrence (such as soft tissue sarcomas) or having residual disease after surgery (haemangiopericytomas). The final is where a reduction in surgical dose is of benefit to preserve function or possibly cosmetics.

There are potential benefits of performing surgery first. These include treating only when it is known that there is residual tumour and increasing the efficacy of the radiation. The down side to it is that there is a chance of spreading cells and all of the surgical site needs to be included, and this can substantially increase the radiation field as well as there being potential areas of hypoxia within the healing tissue bed.

Pre-operative radiation can treat microscopic disease beyond the margins of the resection, the cells may be less viable and decrease the risk of metastasis or seeding, and the regional lymph node can be treated. There can be interference with wound healing.

Intra-operative radiation has been used but has a number of technical problems associated with it. It also only allows one dose of radiation to be given and there is a limit to the dose as a single large dose will increase the rate of late effects and effects on the normal tissues. Some normal tissues can be shielded and so there can be some benefit.

CHEMOTHERAPY AND RADIATION

The advantages are that chemotherapy can act as a radiation sensitiser and increase the effectiveness of the radiation. It is also possible to treat metastatic disease that the radiation alone would not treat. There can be additive toxicities and these need to be considered with individual drugs and the site of the radiation. There is also a problem called recall phenomenon. In this when a chemotherapy agent is given months or years after radiation, there is a recurrence of the radiation injury (often skin changes). This is thought to be due to a depletion of stem cells in the area by the radiation.

BRACHYTHERAPY

This is the use of local treatment with radioactive isotopes. These can be applied to a surface or implanted within the tumour. Those that are implanted can be permanent or removable.

The advantages of brachytherapy are that the tumour receives a higher dose of radiation and there is a reduction in the dose to the normal tissues. The main problems are that there is often surgery involved to implant the devices, the techniques can be difficult, there can be significant exposure to the therapists and the dose can be non-homogeneous.

The permanent implants that have been used include ^{222}Rn which is encapsulated in gold seeds, ^{125}I which has a longer half life and lower dose, and ^{198}Au . The temporary implants include ^{226}Ra , ^{132}Ce and ^{192}Ir . The latter forms can be needles or strings of seeds.

The final form of brachytherapy is ^{131}I which relies on the uptake in the thyroid of iodine compounds after systemic administration and so there is a concentration in that area. This has been used most widely in the treatment of functional thyroid adenomas in cats but also higher doses have been used in thyroid carcinomas in both dogs and cats.

SYSTEMIC RADIATION

This is used rarely in veterinary medicine. There are some radiopharmaceuticals that can be used to treat systemic disease. Samarium has been used in the management of bone tumours or disease with metastases to bone. There can be significant systemic toxicities, especially bone marrow suppression. There is also the

concern of owner exposure and specific management is required. ^{131}I could be considered in this group but it acts more as a brachytherapy. If there is metastatic thyroid carcinoma it can have a systemic effect.

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Canine Lymphoma

Peter Bennett
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Canine lymphoma is a relatively common disease. It is a disease that can provide a diagnostic challenge given the wide range of clinical presentations, but the majority are fairly straightforward. The major differentials to the common presentation of generalised lymphadenopathy are systemic infectious or inflammatory diseases. Most of the infectious diseases that can cause this presentation are not recognised in Australia. Other systemic inflammatory diseases the signs of the inflammation predominate and the lymphadenopathy is found as an incidental finding.

DIAGNOSIS AND CLINICAL FINDINGS

Given the chameleon-like nature of the disease, in theory any patient walking into a veterinary clinic could have lymphoma. But in most cases the owners will have noticed a problem. If a patient presents with a clinical diagnosis of lymphoma the owners should be offered treatment as soon as possible. The patient's clinical condition can deteriorate within a short period of time, but the owners need to have time to consider their options. Cytology is a very good at detecting lymphoma. The pathologists may not be able to be definitive looking only at the cytology, but a clinical picture that is compatible along with supportive cytology is diagnostic. Waiting for about a week to organise a biopsy and histopathology is a delay that can lead to worsening of the patient's condition, at time sufficient to worsen the prognosis.

There are many recommendations for what testing is required in lymphoma patients. My requirements are a minimum of a confirmed diagnosis and a complete blood and urine profile. It is ideal to have a histopathological diagnosis and immunophenotyping as the latter in particular will change the treatments used. There is not great uniformity between pathologists in the histological classification of lymphoma. In most studies this has not been prognostic, but with a more uniform approach some differences might be found. We might also find that different

protocols are better for different classifications. A bone marrow aspirate is the ideal way to confirm if myelophthisis is present. This is not always performed, but if there is a cytopenia present or moderate to large numbers of atypical circulating cells are present then the recommendation becomes stronger. If myelophthisis is present then the risk of myelosuppression increases. Other staging will depend on the signs. If a dog has gastrointestinal signs, then I will recommend an abdominal ultrasound. This is used to try and identify if there is significant gastrointestinal involvement rather than the gastrointestinal signs are secondary to cytokines or other factors such as hypercalcaemia. If there is tumour in the intestine it might not be visible on ultrasound, but generally I do not go to the length of intestinal biopsies to confirm its presence. If there is significant involvement of the bowel it is useful to know as after treatment in these cases a worsening of the clinical signs can arise from drug toxicity, worsening of the disease or in some cases treatment of the lymphoma can lead to some secondary irritation. In the first case protocol modification is needed, in the second a new approach is needed and in the third no alteration is required. Even with pre-treatment screening it may not be possible to differentiate the three, but it is even harder without this information. If there are alterations to breathing then thoracic radiographs or ultrasound is needed. If there is pleural effusion this may need to be drained as a palliative measure. Lung involvement can lead to significant problems when treatment is attempted. Other tests are indicated if there are specific signs of organ dysfunction.

TREATMENTS

Once a diagnosis has been reached then treatment options need to be given. The basics are easy, but there are many options. The standard of treatment is currently combination chemotherapy with a CHOP based protocol. There are several variants of these protocols and all have similar response rates and survival times. The main determinant of which is used is based on familiarity of the treating veterinarian with a specific protocol. Generally speaking the response rate for these protocols is >90% with median survivals of about one year and two year survivals of 25%. Cures are uncommon. Alternative protocols that have been used are the COP protocol (with its many variants) and single agent doxorubicin. These have response rates of about 80% and median survivals of about 9 months. Toxicity rates are similar in all of these protocols.

Variations on these protocols are used in many cases. The major recent change has been for patients with T cell lymphoma. In the past all patients were treated with the same protocol and the patients with T cell disease did not do as well with median survivals of about 3 months shorter than patients with B cell disease. This may mean that T cell lymphoma is more difficult to treat, but it might also mean that we have been using the wrong protocol. In recent years many people have been treating T cell lymphoma with different protocols. A variety of changes has been used but mainly has included more alkylating agents or including a maintenance protocol, or both. Anecdotal information suggests that these changes have improved the outcome to closer to what is seen for B cell lymphoma. No published reports are yet available to confirm this.

Many lymphoma patients will have alterations to the protocols because of toxicities or less than ideal responses. There are no set rules as to which changes should be made and to a degree it will depend on the owner's tolerance of the adverse events. In some cases the dose of drugs do not need to be altered, but pre-emptive coverage for adverse events can be used with drugs such as antibiotics for neutropenia and drugs such as maropitant for gastrointestinal toxicities. In other cases dose reductions or drug substitutions will be required.

Diseases in specific locations may require alterations to the protocols. More many patients with localised disease the best protocols have not been established. In dogs with hypercalcaemia there is altered renal function and an increased risk of gastrointestinal toxicity. Drugs with renal excretion may require dose alteration and drugs with gastrotintestinal toxicities may need to be altered. Nephrotoxic drugs should be avoided. There is some debate on the degree of nephrotoxicity of doxorubicin in dogs with renal changes. There is some risk of nephrotoxicity, but it is low, and this is the single most effective drug that we have for canine lymphoma. Similar considerations are required in dogs with primary renal lymphoma. Dogs with CNS lymphoma should have drugs that cross the blood-brain barrier included in their protocol. If there is significant bone marrow involvement then the concern is myelosuppression. But as these patients are often quite unwell, we also want to use the most potent drugs, which tend to be also the most myelosuppressive. This is a precarious balance and similar dogs may be treated differently depending on cost constraints, the owner's wishes, the rate of disease progression and how well or unwell the patient is at presentation. Supportive care can be used with blood transfusions and covering with antibiotics, but this does not alleviate the risk, it only reduces the risk.

Truly localised (stage I) lymphoma is rare in the dog. When it is seen, surgery alone might be curative. In a few cases of cutaneous epitheliotrophic lymphoma the disease can be again only in one area and surgery or radiation therapy can be curative. In both of these situations it is much more common that while nothing else might be evident on the initial presentation, there is disease in other locations that becomes evident with time. Nasal lymphoma in the dog does not appear to be as often localised as it is in the cat.

There are some dogs that may require no treatment. Dogs with histopathologically proven low grade disease that have no clinical signs can be monitored rather than treated. This is similar to the current recommendations for dogs with chronic lymphocytic leukaemia. In many of these patients, they can live with the disease for a long time (in some cases over a year) with no treatment, and treatment may increase the risk of problems. In most cases the patient will develop clinical signs and a low grade protocol such as chlorambucil and prednisolone can be used. In some patients the onset of clinical signs is an indicator of transformation to a higher grade disease and the standard CHOP or COP based protocols can be used. Patients that have undergone this transformation appear to be less responsive than patients who present with high grade disease as their initial presentation.

In the dog diet has been shown to improve the response to chemotherapy. Low carbohydrate, high fat diet with balanced omega 3 to omega 6 ratios can improve the outcome in patients treated with chemotherapy. The theory behind this response is that lymphoma cells are reliant on carbohydrates as they are ineffective in producing their own, while most cells can generate them from other sources. There is no information that this treatment will help in patients not on chemotherapy, but it is not likely to be harmful. Some dogs will develop diarrhoea if this diet is introduced too rapidly and occasional dogs will have ongoing diarrhoea.

There are a wide range of alternative therapies that have been recommended for use in dogs with lymphoma. Many of these have little scientific basis for their use but at worst are not likely to cause harm. Some may reduce the efficacy of chemotherapy and in some cases they might increase the risk of toxicity. When treating patients with chemotherapy it is important to know if other supplements are being used.

PROGNOSIS

In general the main determinant for prognosis is clinical signs. Those that are well (substage a) have a better outlook than patients that are unwell (substage b). For dogs with generalised disease the median survival is just over a year when treated with combination chemotherapy if substage a and this reduces to about 9 months for substage b. A big question in this information is how to determine where to draw the line between the groups. If one requires no signs other than lymphadenopathy, then there will be very few in substage a. But if the dog is a little lethargic, is taking 50% longer than normal to eat meals, has had some soft faeces or has lost 2% of bodyweight is considered substage b, we may be giving a worse prognosis than is really the case. Most veterinary oncologists will classify a lymphoma patient with very mild signs as substage a. It might be thought that we could have three categories with normal, mildly unwell then moderately to very unwell patients. But now we have two boundaries where we can argue about who is included. And in the end those with mild signs do behave similarly to those with no identifiable secondary signs.

There are many other factors that have been shown to affect outlook. But the majority of these will affect substage. Hypercalcaemia is a good example as most will have moderate to severe clinical signs and so will be substage b.

Stage has generally not found to be prognostic. In some recent work it has been shown that the harder one looks, the higher the clinical stage will be. The increase in stage is usually not prognostic. In some studies stage V has been found to be prognostic, but again many of these patients are clinically unwell. Disease in specific organs such as the kidneys, intestine or CNS will decrease the prognosis significantly.

FUTURE DEVELOPMENTS

Chemotherapy protocols will continue to be tweaked and this will lead to some improvements in outcomes and we may optimise the protocols for some of the sub-classifications of the disease. But the overall difference in outcome will not be major.

Autologous bone marrow transplantation has shown some promise as a means to improve the outcome for dogs with lymphoma. Dogs with bone marrow involvement are precluded from this therapy. This may improve the response and cure rates that have been seen. This is a fairly technically demanding procedure and the ability to

process and store the bone marrow requirements are high. The theory is that bone marrow is harvested, the patient is put into remission with standard chemotherapy and then an intense dose of chemotherapy is given with the toxicities rescued by the use of the bone marrow. The initial studies have been promising, but long term follow is not available for large groups of dogs. The procedure is also expensive. One of the Universities in North America recently offered this as a service and the cost just for the bone marrow collection, processing and storage was \$15,000 USD. For this sort of price I would want strong information that the outcome was improved and the side effects are not greatly increased. The initial results are very promising and if it become more standard of care the cost will reduce, but it is always going to be limited to referral institutions.

The use of a donor bone marrow has also been investigated in dogs. This is a very complex procedure and is more difficult in the dog than in man. If the problems that arise from the current state of knowledge can be overcome, then the advantage is that the treatment could be used in patients with bone marrow involvement including acute lymphocytic leukaemia.

Antibody therapy has been trialled in the past. The initial studies were done over 20 years ago and had some good results. Trials in people have also been shown good responses but many of the antibodies used are specific for one species. Some of the human antibodies are specific for specific mutations that are not present in dogs. But there has been some resurgence of interest in developing canine antibodies so this is an area to watch.

In recent years people have been looking at the use of radiation either to improve the response rate for patients with lymphoma or to consolidate a response. Half body radiation has been used. To date the results have not been consistently different, but with further work on doses used and timing of treatments this may be an option in the future.

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Feline Lymphoma

Peter Bennett
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Lymphoma is the most common malignancy seen in the cat. In Australia FeLV infection has always been lower in incidence than in areas such as North America and Europe, so the types of lymphoma have always been different here.

Lymphoma in the cat is much more variable than in the dog. Specific organ involvement is seen much more often than in the dog. The most common form of lymphoma reported in the cat is intestinal lymphoma. But renal, primary hepatic, nasal and neurological disease is relatively much more frequent than in the dog. As organ involvement usually decreases the prognosis compared to generalized lymphadenopathy, the prognosis in cats is generally worse than for dogs, but there are exceptions.

DIAGNOSIS AND CLINICAL FINDINGS

As in the dog, any cat presenting to a veterinary clinic could have lymphoma. It is rare though for an incidental finding of lymphoma in the cat, whereas it is seen with dogs. The signs of the disease will vary depending on the site of the disease. Concurrent problems are possible in cats with FeLV or FIV infection.

Often the first problem is getting a diagnosis. Unlike in the dog where the patient's presentation will usually allow a clinical diagnosis of lymphoma, this is generally not possible in cats. The typical presentation is that you are presented with a sick cat. As most unwell cats presented with anorexia, lethargy and weight loss, this is usually not helpful. Occasional cats will present with a generalized lymphadenopathy. Unlike in the dog this has a reasonable chance that it is not lymphoma with systemic cryptococcosis, early FIV infection and non-specific reactive lymphadenopathy seen. Cats that have a thoracic mass or abdominal mass are more likely to have lymphoma, but thymoma, FIP and other tumours can have similar presentations.

Fine needle aspiration of nodes or masses can be helpful, but there is more overlap with the other diseases than is seen in the dog. Even generalized hepatic involvement can be difficult to detect on cytology alone as the most common form of hepatitis seen in the cat is lymphoplasmacytic. But in some cases FNA can be diagnostic and with sick patients time is important so this should still be the starting point of diagnostic testing. A complete blood and urine profile is also important.

Gastrointestinal lymphoma is now the most important form of lymphoma in cats worldwide. The most common presenting signs other than those of vague illness are vomiting and weight loss. Diarrhoea is less common. There are two forms of gastrointestinal lymphoma and while they have similar presentations the duration and severity of signs will vary. High grade disease is the most common. This can be diffuse or focal and with the latter a mass effect is commonly seen. In cats the mass can be usually easily palpated. In cats with diffuse disease there is often notable lymphadenopathy and this can be palpable, especially in thin cats. Ultrasound imaging of the abdomen is often suggestive with mass lesions associated with the bowel and associated lymphadenopathy. With high grade disease there is a fair chance of getting support for the diagnosis with a FNA. Biopsy and histopathology is required in many and the options are ultrasound guided or surgical. In cases with a focal mass and little other disease, I feel that these can do better with surgical resection of the mass. This is not curative, but often the patient's clinical condition will improve after the surgery and they seem to tolerate chemotherapy better. Some of the longest surviving cats with high grade intestinal lymphoma that I have seen have had surgery and chemotherapy. For diffuse disease a surgical biopsy will not be palliative and there are risks of poor wound healing in the bowel and an increased risk of complications. Currently there are no recommendations in cats for treating T cell disease differently to B cell disease.

Another common presentation in cats is anterior mediastinal disease. This has been associated with FeLV infection overseas but has also been seen in young oriental cats in Australia. Cats will have vague signs initially but will in later stages show respiratory signs either from the mass itself or secondary pleural effusion. Cats in the former category are often diagnosed on thoracic radiographs when no other causes for illness are found, while the latter group has signs that more readily direct the investigation. Cats with pleural effusion are fragile and need to be handled with care. Some will need oxygen and thoracocentesis before any diagnostics are performed. If unsure if a pleural effusion is present, a single radiograph with no attention paid to positioning is the safest test. The cat is placed on the plate and the radiograph taken with the cat

lying with minimal restraint. The major differential is thymoma. Lymphoma is more common in younger cats and thymoma in older cats, but there is significant overlap. Thymoma can be cystic which is rare with lymphoma. Other masses including thyroid carcinoma, mesothelioma, branchial cysts and soft tissue sarcoma can be seen in this site. FNA is of variable use in this disease as thymoma in cats is a lymphocyte rich tumour and so there is considerable overlap. Ultrasound guided biopsies give a better idea, but occasionally even these are erroneous.

Renal lymphoma in the early stages is often unilateral. The patients are usually vaguely unwell and a dorsal abdominal mass is palpable on examination. In the great majority of cases the disease will become bilateral and renal failure ensues. In a cat with unilateral renomegaly and vague illness there are a number of possible differential diagnoses including polycystic renal disease, pyelonephritis, obstructive disease and perinephritic pseudocysts. Ultrasound is the test of choice to rule out cystic or obstructive disease and a fine needle aspirate can be helpful. The same differentials exist for bilateral disease as all can either cause or be associated with renal failure. Again ultrasound is very useful in ruling out the major differentials. FNA of the kidney is often helpful. In a cat with renal failure, bilateral renomegaly and cytology of the kidney showing large lymphocytes, the diagnosis is extremely unlikely to be anything else. Ultrasound guided biopsies are used where there is any question, but biopsy of the kidney can worsen renal function. As well as the general screening tests urine culture should be included as secondary infections are not uncommon. As part of the initial discussion with most of these clients is the long term management of a cat with renal failure with diet and possibly fluid management.

There are two forms of neurological lymphoma seen in cats. The first is disease within the CNS that presented with typical neurological signs such as seizures, altered mentation and paresis. The second is a disease that affects the peripheral motor nerves, usually those supplying the hind legs leading to lower motor neuron signs to the hind legs. This can appear similar clinically to aortic thromboembolism. The former disease is investigated with typical neurological procedures of neurological examination, advanced imaging (MR) and spinal fluid analysis. A diagnosis is reached in most cases with this approach. For the peripheral nerve disease the spinal fluid is normal and in some cases there are minimal if any changes on advanced imaging. The most common other site in these cases to find disease is in the bone marrow (seen in about 70% of cases) and a bone marrow aspirate can be used to try and make a diagnosis.

TREATMENT

The mainstay of treatment is chemotherapy. There are a small number of cats that present with true stage I disease (disease affecting a single lymph node) where surgical excision is curative. These are uncommon and in most cats where a single enlarged lymph node is found there is disease elsewhere, but not large enough to be seen with current diagnostic tests. Surgery also can play a role in the treatment of focal gastrointestinal lymphoma as mentioned above.

Radiation therapy has limited use in cats. The main site where it has been used is for nasal disease. In some cats nasal disease is part of systemic disease and needs to be treated as such. But in some cases the disease appears to be localized to the nose and regional lymph nodes with long remission seen with radiation therapy only. But these cats need to be fully staged for signs of disease elsewhere before this is used. Again even when staging is clear, disease can show up in other locations. The other area where radiation therapy is used is for dermal epitheliotrophic lymphoma. This rare disease in cats can be localized and hence a suitable disease for this treatment.

There are a range of chemotherapy options for use in the cat. One major difference in the cat is that doxorubicin as a single agent has not been a reliable therapy. Most cats are treated with either a CHOP or COP based protocol. Again there are many variations of both of these options, but each group appears to have similar responses. In the cat it is much harder to assess from the literature the response to treatment. As the cat has much more organ specific disease than is seen in the dog, we would expect variation in the responses depending on the ratio of the different forms of disease in the study. This information is not always available and most studies do not list responses for the various subgroups. There is much less information in the cat about responses relating to immunophenotype. In some studies cats with T cell lymphoma have had better outcomes than those with B cell disease. Currently there are no recommendations for treating the different forms with alternative protocols. Another factor in cats is that some studies only report the cats that responded to the protocols and in the cat it is well known that response, especially a complete response, is a major prognostic factor.

There are several problems that arise in the treatment of cats that have been dealt with in the discussion on the general principles of chemotherapy. These are the increased incidence of anorexia in cats compared to dogs and the at times fractious nature of cats that can make drug administration difficult. Both of these increase the

care needed and the time taken to treat these patients. Some cats are good candidates for placement of vascular access ports, but currently the cost of these precludes the more routine use. These do not preclude treatment, but pre-emptive treatments and sedation are needed more often than in dogs. If the problems of anorexia are controlled, most cats tolerate chemotherapy fairly well.

Gastrointestinal lymphoma is treated based on the grade of the disease. Low grade disease is often responsive to chlorambucil and prednisolone with median survivals of over 18 months reported. For higher grade disease chemotherapy with a CHOP or COP based protocol is used with or without surgery. In the early stages some caution is required in the use of oral medications as absorption may be reduced. The cats' high natural requirement for cobalamin might also need to be addressed as it can be in cats with inflammatory bowel disease. The presence of pre-existing gastrointestinal disease can increase the risk of exacerbation in some cats. Weight loss, cachexia and anorexia are often present and nutritional support can be a critical part of the early management including in some patients the placement of feeding tubes.

In cats with renal lymphoma there is altered excretion of some of the drugs, many cats are systemically unwell and gastrointestinal signs are not uncommon in cats in renal failure. All of these will alter the risk of complications with chemotherapy. The more intense the supportive care in the initial phases, the fewer the complications that are seen. Intravenous fluids and gastric protectants are useful. In some cats there can be restoration of renal function when the lymphoma is controlled. Most of these cats will have mild to moderate azotaemia at presentation. Cats with severe azotaemia are very unlikely to return to normal. Renal transplants are not a viable option for these patients as when this has been tried, lymphoma appears in the implanted kidney in most cases. Doxorubicin has been shown to be nephrotoxic in experimental studies. It has not been clearly documented in clinical situations. Many oncologists recommend that in the CHOP protocols mitoxantrone is substituted for doxorubicin.

Neurological lymphoma treatment is complicated by the need for drugs that can cross the blood-brain barrier. In the early stages this is less important as this barrier is not likely to be intact, but this can be an issue when remission occurs. The main drugs that cross the blood-brain barrier are CCNU and cytosine arabinoside. As the barrier extends to the major nerves, this needs to be a consideration in some cases with peripheral nerve disease also. CCNU has been used as a single agent or the two used together. In other patients the

standard protocols are altered to include one or both of these drugs. No clearly superior treatment protocol has been established.

Cutaneous epitheliotrophic lymphoma in the cat is very uncommon to rare. CCNU has been the most effective treatment in dogs and has been used in cats. For early lesions linoleic acid has been used. Retinoids that have been used with occasional success in dogs are associated with significant toxicity in cats.

In all forms of lymphoma palliation can be achieved with prednisolone. As with more definitive treatment there is variation in the success. But 50 to 75% of patients will have improvement in clinical signs for 1 to 2 months. Long term survival (> 1 year) is seen occasionally. I will typically use a dose of 5mg BID for most cats, occasionally 10mg BID for large cats. With response I may reduce this to SID, but rarely drop below this dose unless there are problems.

PROGNOSIS

There is a wide variety of prognoses for cats with lymphoma. The location and response to therapy are the major determinants. Low grade GI disease and nasal lymphoma has the best outlook (median survival 18 months) followed by generalized lymphoma (median survival 9-12 months). Renal and neurological have the worst outlooks with median survivals of < 6 months. In all cases the severity of illness on presentation will alter the outlook. I will subtract 25 to 50% from the median in moderately to severely unwell patients.

Cats that have a complete response will do better than cats with partial remission. It has been recommended by some that treatment is only continued in cases that have complete remission, but I do not practice this. As in the dog, pre-treatment with glucocorticoids will reduce the prognosis with lower remission rates and duration.

The amount of supportive care that is given to the patient will have some influence on outcomes. The more that is given, especially in a pro-active manner, the better the outcome. But this is not a viable option for all clients.

FUTURE DEVELOPMENTS

There are no major developments on the horizon for cats with lymphoma. Bone marrow transplantation has yet to be investigated

to any degree. People are still looking at the older protocols and making some alterations, but these are having only minor differences in outcome. People have reviewed some of the protocols that have been used for a long time and the more recent work has shown improved outcomes. The drugs are the same, so it is likely that the major difference is the improvement in supportive care, early management of toxicities and increased knowledge of the protocols. Some of the changes are likely to have arisen due to the altered incidence of FeLV infection since the introduction of a vaccine. But this does not explain all the changes seen.

NOTES:

Mast Cell Tumours

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Mast cell tumours in the dog are relatively common skin tumours. In the cat the disease is much less frequent and the visceral form of the disease is seen as often as the cutaneous form of the disease. This is a disease that causes lots of problems because of the diverse presentations and biological behaviour noted, especially in the dog.

In recent years more information has been found for mast cell tumours. A lot of this relates to the push in human oncology for specific mutations in tumours cells and the c-kit mutation seen commonly in canine mast cell tumours is one of interest. This has lead to the development of some novel treatments.

CLINICAL PRESENTATION AND DIAGNOSIS

In the dog most mast cell tumours will be dermal or subcutaneous lumps. Some cases can appear as a diffuse dermatitis. The mass lesions can imitate any other skin mass including lipomas and skin tags. The more typical aggressive lesions with associated swelling or ulceration are easier to identify. It would not be unwise to treat all skin lumps on a dog as if they were a mast cell tumour until proven otherwise.

The granules of mast cells contain histamine, serotonin and heparin, which lead to some of the typical signs. If irritated the release of histamine can cause a significant swelling within minutes, that can resolve quickly also. They can also bleed easily and it can take a long time for the bleeding to stop in some cases, occasionally days after a biopsy. These chemicals also will delay wound healing that can be a concern when trying to get a biopsy and also if marginal excision is tried.

Mast cell tumours are usually solitary on presentation, but in about 10% of patients they will be multiple. In dogs with multiple tumours the numbers can range from a couple to lots. The presence of multiple tumours is not associated with systemic disease and the

outlook is similar to single tumours. So when a mast cell is identified, the next step is to look for the next one.

Fine needle aspiration is a very useful tool in the investigation of any skin lump, especially mast cell tumours. In most cases the granulated cells are readily identified and often there is an eosinophilic infiltrate. Some high grade tumours have very poorly granulated cells so identification is difficult, but complete absence is unusual. With poorly granulated cells Diff-Quick is not as good at identifying the granules than the commercial stains used at a laboratory. Grading of the mast cell tumour is not possible with cytology. The use of other stains to identify AgNORs, c-kit mutations, proliferation markers have been used on cytology samples and these can come close to identifying the grade of the tumour.

Biopsy is recommended in all cases of cutaneous mast cell tumour. The grade will predict what staging is ideal and what margins should be taken. In areas where wide margins are easily taken, such as the flank, this step can be missed, but it should be recommended. In areas where difficult or major surgery is required, the recommendation should be very strong.

It is never wrong to stage a dog with mast cell tumour. There are many times when finding metastatic disease will alter the recommendations. The ideal staging is to sample the local and regional lymph nodes, abdominal ultrasonography and thoracic radiographs. Buffy coat examination and bone marrow aspirates can also be used. The former is easier to perform and is very sensitive, but it is poorly specific. A bone marrow aspirate is less specific, but is highly specific. My preference in these cases is to perform a bone marrow aspirate. There is a bit less impetus to grade a very low grade tumour and more with mid to high grade tumours. But it is a combination of grade and local treatment options will determine the utility of staging. A very high grade tumour will have a recommendation for adjunctive chemotherapy so finding small amounts of disease in a distant location will have little effect. In a dog that requires an amputation or major reconstructive surgery then that little bit of disease will have more impact on the management. For tumours in areas with limited tissues local staging should be considered to more accurately plan the margins. MR is the tool of choice as this has the best definition of soft tissues.

There are a small number of dogs that present with systemic disease. This can be seen in conjunction with superficial disease or purely internal. The former is usually more easily identified. The systemic disease can be metastasis from the skin disease or the skin mass might be metastatic. These patients are systemically unwell.

While gastrointestinal signs can occur with superficial disease it is unusual, while it is common for systemic disease. Staging should always be performed in systemically unwell patients not matter what the grade of the skin tumour. Systemic disease can occur anywhere. While most often in lymph nodes, spleen and liver it can be found in any organ including the lungs and nervous system. When systemic disease is suspected and there are no obvious locale found, then aspiration or biopsy of the spleen and liver should be included in the screening process.

In the cat there is about equal frequency of skin and systemic disease. The skin disease more often involves the head and neck and Siamese cats seem predisposed. The lesions are usually dermal, raised, erythematous with alopecia. The granules do not stain as readily as those in the dog and histological grading has not been shown to be useful. They act benignly in most cases but assessment of the regional lymph nodes is recommended. As in the dog, it can be associated with systemic disease, but in these cases the signs of the systemic disease usually predominate. There is a histiocytic form that can spontaneously regress. Systemic disease in the cat is often associated with the spleen or intestine. Gastrointestinal signs are common and can be severe. Ultrasonographic changes are common and fine needle aspiration is usually diagnostic.

TREATMENT

The treatment of mast cell tumour in the dog will depend on the grade and stage. Localised disease is the most common form seen. The treatment of choice for localised disease is surgical removal with wide (2-3cm lateral, 1-2 fascial planes deep) margins from all the gross tumour. Wide and complete excision at the first surgery has the best outcome. If margins are close or dirty then repeat surgery will need to be from the surgical bed, not the previous tumour location. Pre-planning with local staging and preparation for grafts or flaps needs to be in place if they are needed. Narrower margins are used for low grade tumours with a low mitotic index, with wider for high grade or high mitotic index tumours. Incomplete excision (de-bulking) in most cases is associated with a high risk of morbidity and rarely leads to a meaningful benefit.

Radiation therapy is useful for localised disease. For small tumours it can be used as a sole therapy. For large tumours responses can be seen but they are more likely to be short lived. Radiation can be used in conjunction with marginal surgery to reduce the surgical dose required. There are arguments as to which modality should be

done first. The radiation oncologists recommend radiation as after surgery there are areas of hypoxia that will decrease radiation efficacy. The surgeons will recommend surgery as there is a higher risk of wound complications when surgery is done in an area that has been irradiated.

A number of chemotherapy protocols have been used in dogs with mast cell tumours. The early responses were poor, but recent reports have shown a lot of improvement. The protocols that have shown benefit include CVP (vinblastine, cyclophosphamide, prednisolone), vinblastine and prednisolone, Lomustine (CCNU), Lomustine and vinblastine and Lomustine, vinblastine and prednisolone. Initially chemotherapy was used for systemic disease. But more recent studies have also shown benefit in reducing the risk or delaying local recurrence after marginal resection (used as a substitute for radiation), pre-emptively treating high grade tumours and prior to surgery to down stage the patient. Currently I am using a Lomustine and vinblastine combination in all of these situations.

Prednisolone has been used in the past for a number of reasons. There was one early study that recommended the use of prednisolone for at least six months after surgical removal of grade II mast cell tumours. When this was re-evaluated more recently, there was no benefit shown. I am also concerned that the prednisolone will reduce the early signs of recurrence or of a new tumour and delay diagnosis. A more recent paper discussed the use of prednisolone to down stage a tumour prior to surgery. The paper showed success in decreasing the tumour size and hence the surgery, but there was no long term follow up to look at recurrence rates. It is possible that microscopic areas of mast cell tumour remain in the tissues and might increase the risk of recurrence. I do not recommend either of these options.

Palliation is the time when I do use prednisolone, usually in combination with anti-histamines. I will use new generation H1 blockers for swelling and irritation and H2 blocker or omeprazole for gastrointestinal signs. Chemotherapy is the most effective palliation for systemic disease, but it does not always work. These options are also the ones that I use in cats.

In cats with skin disease, surgical resection is the treatment of choice. Wide margins do not appear to be needed. The histiocytic variant may resolve so no treatment might be needed. There is limited information on the use of radiation, but it does seem to be effective. Chemotherapy has been used with some success for systemic disease. CVP, vinblastine and prednisolone and Lomustine have been used. Responses can be dramatic but long term survival is uncommon. The exception is a subgroup of cats

that have splenic involvement. A subgroup of these cats will have evidence of disease elsewhere (liver, lymph nodes, gastrointestinal tract) but the disease will resolve post splenectomy. This does not happen in all cases and currently there are no clear guidelines to help in the decision making. Having the majority of the disease in the spleen appears to be the main criteria identified to date.

PROGNOSIS

The prognosis will depend on the grade, stage, mitotic index, treatment used and clinical stage. The lower the grade and mitotic index the better the outcome. First time complete excision with good margins will improve the outcome. The use of radiation for marginally resected tumours will improve the outcome. The use of chemotherapy in patients with high grade or high mitotic index tumours will improve outcome. Recurrence of a tumour, inadequate excision, metastatic disease present, no systemic treatment use in high grade tumours will all diminish the outcome.

But no current knowledge allows us to predict what will happen in an individual. A dog with a grade I tumour, complete excision and low mitotic index can have disease in the regional lymph nodes within a months while a dog with a grade III tumour that has been present for two years with no treatment will have no distant disease. It is this failure to identify what will happen in an individual that can lead to frustration and confusion for all concerned.

FUTURE TRENDS

Further evaluation and development of chemotherapy and radiation protocols may lead to some improvement in outcomes. A dramatic change is not likely to occur. A new drug or combination is not likely to make a major difference but the current recommendations need to be optimised.

Mast cell tumours have benefited from the development of small molecule inhibitors. Kinavet and Palladia have been released in Europe and North America for use. These drugs target the c-kit mutation and block some of the downstream effects. They are not specific for this target and will have some effects on VEGF and PDGF receptors also. They are used in similar situations to chemotherapy and are not a panacea. They do not work in all patients, they can take a long time for an effect to be seen and they still have side effects. Palladia has gastrointestinal side effects in

up to 50% of patients (usually mild) and neutropenia has been seen.

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Soft Tissue Sarcoma

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Soft tissue sarcoma is a common tumour of the skin and subcutis in dogs. In the cat it is less often seen, but the injection site sarcoma is an important, if uncommon, form of this disease and so will be dealt with separately. This is a group of tumours that we group together because they share similar clinical and behavioural characteristics. The group includes fibrosarcoma, haemangiopericytoma, peripheral nerve sheath tumours, leiomyosarcoma and liposarcoma. There are some sarcomas of soft tissues that are not included routinely in this group because their behaviour is very different. These include haemangiosarcoma and synovial cell sarcoma.

CLINICAL PRESENTATION AND DIAGNOSIS

The primary clinical presentation of cutaneous soft tissue sarcoma is a firm, often poorly defined, mass in the subcutaneous or dermal tissues. They can be small to very large. Some in the subcutaneous tissues can be soft and can be indistinguishable clinically from a lipoma. The masses are usually not irritating, ulcerated or inflamed. In some cases they can cause mechanical interference if they are large enough or infiltrate into the soft tissue surrounding a joint. Systemic signs are very uncommon.

The behaviour of these tumours depends on their grade. They are all locally invasive, but they are more invasive the higher the grade. The exception to this is haemangiopericytoma that can be highly invasive (sometime >3cm), no matter what grade. The risk of metastasis ranges from about 5% for grade I tumours to close to 50% for grade III tumours. Recent work has also identified that location can predict behaviour with tumours distal to the carpus or hock that were low grade and had low mitotic indices were less likely to recur than lesions in other locations.

Once more the first step is to get a firm diagnosis. Fine needle aspiration has less value than for other tumours as sarcoma cells do

not always exfoliate readily. But it is useful in ruling out some of the differentials including lipoma and mast cell tumours and at times it can be diagnostic. A biopsy is the preferred option and this is the only means by which a histological grade can be gained. Biopsies can be obtained surgically, but can also be collected with core needle biopsy instruments or even dermal punches. Care must be taken when collecting a biopsy that the biopsy site can readily be removed at the time of definitive resection. Very small samples can limit the ability of a pathologist to grade the tumour and in some cases the tumours can be heterogenous. As the worst case is always taken as the grade, the tumour will not be graded higher than it should, but some areas might lead to a grade lower than it should be.

Once a tumour has been identified as a soft tissue sarcoma and a grading made, then the next step is staging. Once more it is never wrong to grade a patient with a soft tissue sarcoma and on rare occasions the skin and subcutaneous lesions are metastatic from an internal primary. For low grade tumours staging is unlikely to be positive, but it should be mandatory if major surgery or reconstruction is required. The ideal staging involves regional lymph node aspiration, thoracic imaging (radiographs or CT) and abdominal scanning (ultrasonography or CT). Local staging can be extremely important in planning surgery. Failure to adequately plan is the major reason for failure.

The primary presentation of internal soft tissue sarcoma is much more variable. In some cases presentation can be very late as there are often few systemic signs. In some cases the presentation can be because of organ dysfunction, usually obstruction, haemorrhage or paraneoplastic syndromes. Some cases will have vague presentations including weight loss. Thoracic masses can lead to pleural effusion and the signs would relate to that. The paraneoplastic syndrome most often associated with these tumours is hypoglycaemia associated with mainly smooth muscle tumours. Obstruction of any of the tubular organs is possible.

Diagnosis can be more difficult in cases with vague presentation, but a mass is usually found during general screening. The nature of the mass might not be clear and so sampling, usually a biopsy, is required. As with the superficial lesions, a diagnosis is required as the treatment options may change if we know that the mass is indeed a soft tissue sarcoma.

TREATMENT

The primary treatment option is surgical resection. For the majority of the low to middle grade sarcoma this will can lead to cure if the resection is complete. As was mentioned in the general approach, the first surgery is the best chance of cure so this must be planned carefully. This applies whether the mass is superficial or internal. Incomplete resection and recurrent tumours are a major risk to the patient. Many of these problems arise when a diagnosis was not made prior to surgery. The surgery needs to be aggressive with at least 2-3cm margins laterally and two tissue planes deep. For haemangiopericytoma, 5cm lateral margins have been recommended. In areas with limited scope to wide surgery narrower margins can be taken if adjuvant therapies, mainly radiation, are used. Radiation used in this way will improve the outcome but the results are not as good as complete resection. Chemotherapy has been used in this way, but there is little published about its use. Generally surgery is followed by radiation, but some have advocated that radiation be used first to reduce the size of the mass, but there are potential problems with this approach. Chemotherapy has been used to down stage tumours prior to surgery with some successes, but the rate of response is not well reported.

A recent report on marginal excision of low grade soft tissue sarcomas with low mitotic indices located on the distal limbs had a good outcome with a lower than expected recurrence rate. This has lead to some re-evaluation of recommendations for tumours in these locations. Also, as many of the previous studies using radiation post surgery included reasonable numbers of these patients, the results may have been positively biased by this tumour behaviour.

Radiation therapy has been used as a sole therapy. Reasonable response rates and long term control have been seen. But the chance of cure is lower than for surgery. This is generally well tolerated and is most often used when the tumour is located in such as way as to make resection difficult or be associated with significant morbidity.

Chemotherapy has been used occasionally. It has been used as a sole therapy in patients with metastatic disease or in situations where radiation therapy is ideal, but is not available or is declined. The measurable response rates are fairly low (20-30%) but with some other cases having some control of growth noted. Both standard full dose chemotherapy and metronomics have been used. The latter has had some surprisingly good responses in a small number of patients. The use of chemotherapy for high grade

tumours after complete resection is still questioned. Few studies have looked at this and no clear improvement in outcome has been seen. But the studies to date have been retrospective and this may have lead to a bias. If the patients that the clinicians thought were most likely to have metastatic disease were pushed more firmly to have chemotherapy and less so for the more borderline cases, then the studies will be biased for a worse outcome in the patients selected to have chemotherapy. It would be good to have this looked at in a large prospective study.

In internal tumours where there has been haemorrhage or there is a high risk of haemorrhage, then surgical resection is the treatment of choice. In many of these cases complete resection is not possible and so adjunctive therapies are needed. Intra-operative radiation has been used, but has limited application due to the single dose given. External beam therapy is more difficult and now only with the latest machines the incorporate a CT, can this methodology be used. Generally chemotherapy is the adjuvant therapy of choice. In patients where the main problem is an effusion, then some of these can respond to intracavitary chemotherapy. This can control the effusion and allow time for systemic chemotherapy to have some chance of controlling the tumour.

PROGNOSIS

The outlook is excellent for low grade tumours without evidence of metastasis that have been completely resected. For incompletely or marginal moderate grade tumours then adjuvant radiation therapy can improve the outlook. For low grade tumours on the extremities the outlook is fairly good. For high grade tumours or non-resectable tumours the outlook is guarded to poor.

Recurrent tumours can act more aggressively then the original tumour. There are a number of factors that play a role. The main one seems to be the cytokines that are involved in wound healing can act as tumour promoters. There are also areas of hypoxia in a wound bed and this has also been shown to promote a more malignant phenotype.

Another tumour that warrants special mention is the histological low grade, biological high grade fibrosarcoma seen on the face of dogs. These aggressive tumours have almost benign histology. Currently few responders to surgery, radiation or chemotherapy have been reported. A few patients treated with metronomic chemotherapy have had relatively long survivals. It may be that anti-angiogenic therapy is the best option for managing this disease.

INJECTION SITE SARCOMAS IN CATS

These have been well described over the years and have most often been associated with rabies and FeLV vaccine sites. The risk is low (1 in 10,000-100,000) but when it does occur it has dramatic effects. The exact cause is unknown and although the adjuvant used in these vaccines has been implicated, the reason is not known. The disease has been seen with other injections including program, antibiotics and a microchip. Cats have been known to develop malignancies at sites of chronic inflammation and one classic disease is the formation of osteosarcoma in an eye after a cat fight injury.

This does not mean that cats should not have injections. But careful consideration to the value of the injection should be given. FeLV vaccine is quite effective and has reduced the incidence of FeLV-related disease where it has been used. But in areas where the rate of infection is low, then the risk may outweigh the benefits. Even with an antibiotic, does the injection at the start of a course really make a difference?

It is advisable to warn owners of potential problems and to get them to watch the site of any injection. Cats will often form a bit of a lump at an injection site but this should go away with a few weeks or so. Any lump that persists for three months is a concern. The recommendation for FeLV and rabies vaccines is that any post vaccinal lump that is still present at three months should have a biopsy taken. There is no reason that similar recommendations should not apply for other injections. It has also been recommended that these vaccines be given on the hind legs as this is a much easier area to perform wide surgery on than the interscapular area which is the easiest site in cats to give an injection. Maybe any depot injection in cats should be in these sites.

FUTURE TRENDS

As these tumours also cause problems in human oncology there has been some interest in the use of dogs as models for human disease, but not a lot of information has become available yet. As the use of targeted therapy becomes more widely available, more information is needed. Some of these drugs alter the metabolism of a tumour but do not alter its size, so standard monitoring tests are not applicable. Newer modalities are being developed, often involving

PET scanning. As newer markers are developed then it has to be shown that they indicate what is happening in a tumour and that the new drug is doing what they think it is doing. The best way to assess this is with serial biopsies. This is hard to do in human patients, but as dogs require a general anaesthetic for a PET scan, serial biopsies for these tests would be possible.

For low grade tumours there will not be a lot of change for the foreseeable future. Wide excision will remain the treatment of choice. Most of the recent advances have involved improvements in local staging with the more widespread use of advanced imaging, especially MR, and also improvement in surgical techniques to repair more difficult deficits in patients. Minor improvements in outcome will come with optimisation of radiation protocols.

For high grade tumours there are some options. Chemotherapy may play some role. The use of some of the small molecule inhibitors has had some responders. Palladia has been used for gastrointestinal stromal tumours that have a c-kit mutation, and for other tumours as they often have VEGF or PDGF receptor mutations. As more small molecule inhibitors are developed, some will have application for our patients.

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NOTES:

Gastrointestinal Tumours

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Tumours of the gastrointestinal tract are moderately common in the cat, especially lymphoma, and uncommon in the dog. They are a diverse range of tumours and have a variety of outcomes. Generally the presentations are similar but the management will vary depending on the diagnosis. The management of intestinal lymphoma has been covered in the lymphoma section and will only be touched upon here.

The diseases frequencies and recommendations for management will vary between the dog and the cat. The presentations also can have some differences. But the general principles apply to both species.

CLINICAL PRESENTATION AND DIAGNOSIS

Oral tumours deserve a whole session to themselves. They are fairly common with squamous cell carcinoma seen most often in the cat and melanoma and squamous cell carcinoma the most common in the dog. In some cases the owners will notice a mass in the mouth, more often they will see trouble eating or drinking, bleeding, halitosis, or a swelling on the side of the face. Other than the very caudal tumours a diagnosis can be made often on physical examination, though at times sedation is needed for caudal tumours and early squamous cell carcinoma can mimic gingivitis. In the cat most tumours will be malignant. In the dog epulides and gingival hyperplasia will overlap with some of malignant tumours. If there is any suspicion then a biopsy should be taken as the first step. This will then indicate if staging is indicated or if benign local resection is all that is required.

Careful examination of the mouth often requires sedation or anaesthesia. In most cases if the tumour is overlying bone, the bone will be involved. Especially for maxillary tumours advanced imaging (MR or CT) is strongly recommended including for acanthomatous epulides. Radiographs of the affected area at least

should be done. Thoracic radiographs and aspiration of the regional lymph nodes should be undertaken in all cases of malignant tumours. In the dog oral plasma cell tumours are seen uncommonly. These can be isolated disease and act benignly or occasionally will be part of systemic plasma cell tumour or multiple myeloma. In these cases as well as lymph node aspirates and thoracic radiographs, radiographs of the flat bones, abdominal ultrasonography and a bone marrow aspirate should be considered to rule out systemic disease.

Oesophageal tumours are very uncommon and the signs will be of regurgitation. This can be hard to recognise and many owners will report that the patient is vomiting. Thoracic radiographs can show a secondary megaesophagus proximal to the tumour and occasionally a mass lesion can be seen especially if the lesion is caudal to the heart. Endoscopy does not always identify a lesion unless the mucosa is involved. Endoscopic biopsies have a low diagnostic rate. Contrast radiography can be useful in showing a persistent filling defect, but this finding can easily be over interpreted. Thoracic CT can be used in some cases.

The obvious is that tumours of the abdominal intestinal tract and stomach will usually present with gastrointestinal signs. Vomiting, diarrhoea, weight loss, anorexia, nausea, tenesmus and protein loss can all be seen. The combination of signs in an individual will vary depending on the tumour type and location. Blood can be seen in either the vomitus or diarrhoea and melaena can also be seen. The presence and type seen will depend again on the both tumour type and location.

There are some cases where the clinical signs can be vague with loss of appetite as the main finding. There are some cases where they will present with an abdominal effusion which can be a malignant exudate, a modified transudate secondary to lymphatic obstruction or a transudate secondary to hypoproteinaemia. In the majority of cases there are clues that will send investigations towards the abdomen.

Abdominal ultrasonography is a very useful tool in the investigation of these diseases. A mass lesion is often present or lymphadenopathy. Diffuse lymphoma or mast cell tumour are the diseases that have the more difficult lesions to identify. If a lesion is identified then fine needle aspiration can give some clues as to the nature of the disease. Lymphoma, mast cell tumours and carcinomas will all tend to exfoliate reasonably well. The sarcomas are less common and this may not be identifiable. If the lesions are large enough then a biopsy can be taken. If the lesion can be identified to be in the stomach or proximal duodenum then endoscopic biopsies can be utilised. This is not appropriate for

muscle tumours. Surgical biopsies may be needed and in most cases this is often a combined diagnostic and therapeutic tool. Surgical biopsies carry much greater risks in patients with hypoproteinaemia and if the colon is involved.

In any patient where abdominal neoplasia is known or suspected they should be evaluated for metastatic disease as most are malignant. Within the abdomen the lymph nodes, the liver and spleen should be carefully evaluated. Aspirates or biopsies of suspicious lesions can be undertaken under ultrasound guidance. If abdominal CT is used then it is more difficult to aspirate a lesion and in many cases the lesions are not related to the tumour. Thoracic radiographs are indicated in all cases other than suspect lymphoma.

Rectal tumours most often cause tenesmus and fresh blood in the stools. The stools are often either flattened or ribbon like. Constipation can occur secondarily. Some rectal tumours are circumferential and can mimic a rectal stricture. Rectal examination will detect most of these tumours. Staging is as for other intestinal tumours and a biopsy can often be taken by exteriorising the tumour and taking care not to perforate the bowel. Colonoscopy is recommended in all cases to assess the length of the disease and if there are lesions more proximally. Diffuse or multifocal disease is not as common in dogs and cats as it is in people.

Anal sac tumours are seen with some frequency in the dog and are rare in the cat. These can cause local irritation and tenesmus. Constipation can occur and I have seen this more often with enlargement of the sublumbar (mainly the hypogastric) lymph nodes rather than the primary tumour. Hypercalcaemia is seen fairly often as a paraneoplastic syndrome and it is not uncommon for a patient to present with signs related to the calcium (PU/PD, lethargy, vomiting, etc) rather than signs relating to the primary tumour. In some cases very small tumours (a few mm) can lead to significant hypercalcaemia.

These tumours are usually readily identified on rectal examination. Care must be taken to empty the anal sacs before completing the examination. Enlargement of the hypogastric and pelvic lymph nodes can be identified where present in most dogs. Fine needle aspiration of the mass is often diagnostic. Other tumours including squamous cell carcinoma have been seen. Staging involves abdominal ultrasonography and thoracic radiographs.

TREATMENT

Oral tumours are treated with surgical resection if they are benign. For acanthomatous epulides bone needs to be removed to avoid recurrence. For large acanthomatous epulides radiation therapy has been shown to be effective.

The malignant tumours are managed differently depending on the diagnosis. In the dog squamous cell carcinoma has a low metastatic rate unless the tongue or tonsils are involved. Surgical resection is the treatment of choice with wide margins. Radiation therapy either as a sole therapy or following marginal excision has been shown to be effective, but not as good as complete resection. For tonsillar squamous cell carcinoma surgical excision is often difficult but marginal excision can be performed. Adjunctive radiation and/or chemotherapy is highly recommended and long term survivals have been seen. Chemotherapy has been used as a sole therapy where surgery is not possible and radiation is either not available or it is declined by the owners. Some sustained responses have been seen.

In the cat oral squamous cell carcinoma can occasionally be resected with wide margins. The response to radiation has been less effective than in the dog but with some improvement with some different protocols recently reported. But most do not do well. Chemotherapy traditionally has not had much effect but recently some good responses have been seen with combination chemotherapy, but the response rates remain relatively low.

Oral melanoma in the dog is best treated with a combination of surgery and chemotherapy. This disease has a high metastatic rate and local therapy is usually not curative. Small lesion that are rostral and with a low mitotic index can be cured by surgery alone, but these are not common. The surgical resection does not have to be as aggressive as that for squamous cell carcinoma, but if the lesion is overlying bone, then bone should be removed to assure clean margins are achieved. While no clear ideal chemotherapy protocol has been established, carboplatin, usually with piroxicam, has had some good results. Radiation therapy has been used to treat the local disease with some success. Course fraction protocols and with the use of chemotherapy sensitisers has shown some good local responses, but systemic treatment is still recommended for metastatic disease. Recently there has been a limited release of a vaccine in North America. This has shown some success in controlling metastatic disease after resection of the primary tumour. Trials are still ongoing and currently there is no indication of when this would be available in Australia.

Oral fibrosarcoma has a low metastatic potential and is treated with wide surgical resection. Plasma cell tumours on the gingival in dogs are usually benign and cured with complete resection. Mandibular osteosarcoma is seen with some frequency in dogs and has a better prognosis than for appendicular disease, but still will metastasise in about 50% of patients and treatment is ideally local resection and followed by chemotherapy.

Oesophageal tumours are difficult to treat. Smooth muscle tumours (leiomyosarcoma or leiomyoma) are the most common tumours seen. In areas where *Spirocerci lupi* is endemic there are carcinomas seen secondarily to the parasite. Squamous cell carcinoma is the most common carcinoma seen. In patients where the lesion is small then in some cases surgical resection can be undertaken. Larger resections have been reported with transplantation of a segment of small intestine to replace the deficit with fairly poor outcomes. There are no reports of chemotherapy and the chances of a clinically significant response would be fairly low.

Gastric tumours are best treated with surgical resection, but this is not often possible. The most common site of carcinoma is on the lesser curvature and as this is where the source of the blood supply runs, wide excision is usually not possible. Tumours of the antrum and pyloric areas are sometime amenable to resection, but there is significant risk of complication with the reconstruction needed. While there are no firm recommendations for chemotherapy some responses have been seen for both carcinomas and sarcomas to combination chemotherapy. For carcinomas and high grade sarcomas adjuvant chemotherapy should be considered to deal with metastatic disease.

Intestinal tumours are usually amenable to resection and there are similar recommendations for adjuvant chemotherapy. There are no published reports on the best options and how much improvement in outcome is seen, but there is anecdotal information to suggest that outcomes are improved. The currently protocols considered for carcinoma are a combination of carboplatin with 5-fluorouracil or gemcitabine. A doxorubicin based protocol is used for sarcomas. Recent work has shown that dogs get gastrointestinal stromal tumours. These are histologically identical to leiomyosarcoma and are identified as they have a c-kit mutation. Some of the small molecule tyrosine kinase inhibitors used to treat mast cell tumours (Palladia, Kinavet) may have a role in the management of this disease, but no work has been done yet.

Rectal tumours are difficult to resect and pelvic splitting may be required. There has been some response of these tumours to

piroxicam as a palliative and the use of chemotherapy as a sole therapy or as an adjunct should be considered.

In dogs with anal sac tumours the initial treatment will depend if hypercalcaemia is present. This needs to be addressed with some urgency with intravenous fluids and supportive care. If the tumour is localised then surgical resection is indicated. This can include removal of the sub-lumbar lymph nodes. This can be difficult and there is a high degree of morbidity and risk of death. The nodes need to be few in number and relatively small to contemplate this surgery. Complete resection is usually not possible due to the location. I will usually consider margins to be dirty. After resection the next consideration is for adjuvant therapy. I recommend chemotherapy in all cases as metastatic disease is highly likely and there can be some control of the local disease. Carboplatin or mitoxantrone are the drugs most often used. Radiation therapy of the tumour site and the sublumbar nodes either alone or with chemotherapy has shown some success. There is a fairly high complication rate for radiation in this area and megavoltage therapy is usually required.

There are some patients with intestinal tumours, usually carcinomas, which present with a malignant abdominal effusion. This effusion can cause as many problems as the primary disease. There are some patients without an effusion but at the time of surgery widespread small metastatic lesions are seen throughout the peritoneum (carcinomatosis). In both of these situations the use of intracavitary chemotherapy can be very effective in controlling both the effusion and the superficial disease. The exact mechanism of control of the effusion is not known as in many cases there is no measurable tumour response. The high concentration of the drug at the site of the tumour can be more effective than systemic chemotherapy in controlling disease. Cisplatin is the drug of choice for dogs and carboplatin for cats.

PROGNOSIS

For oral tumours the outlook depends on the type of tumour and treatment. For squamous cell carcinoma the outlook is good if the tumour has been completely resected. In the dog the prognosis is guarded for tonsillar or lingual tumours. In the cat the outlook is generally guarded to poor as complete resection is usually not possible. The outlook is good also for fibrosarcoma with complete resection. For melanoma the outlook is good for small, non-ulcerated tumours with a low mitotic index after complete resection. For the majority the outlook is guarded.

For oesophageal tumours the outlook is poor to grave. Gastric tumours typically have a poor prognosis. Intestinal sarcomas can have a reasonable outlook after resection for low grade disease and guarded for high grade disease. The prognosis for carcinoma is generally guarded to poor. Rectal tumours have a guarded to poor outlook.

Anal sac tumours have a guarded outlook. The outcome tends to improve when more aggressive treatment is used. Treating the local disease, the regional lymph nodes and systemically has the best outcome. Surgery alone has the worst outcome other than no treatment at all. Dogs with hypercalcaemia in most studies have not done as well as those whose calcium is normal.

FUTURE TRENDS

There are a number of fields where newer treatments may play a role. The use of vaccine in the treatment of oral melanoma is likely to become more widely available. The use of small molecule tyrosine kinase inhibitors may have a role in treatment of a number of tumours including mast cell tumours, gastrointestinal stromal tumours and sarcomas.

NOTES:

Paraneoplastic Syndromes & Palliation of the Cancer Patient

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Cancers can affect patients in a variety of ways. The most obvious is a direct effect of a tumour. For example a brain tumour leading to seizures or an intestinal tumour leading to vomiting or diarrhoea. They can have secondary effects through bleeding or paraneoplastic syndromes. Finally, when we treat the patients there can be toxicities and problems associated with the treatments. As many cancer patients are older, they may have concurrent disease that can have effects on their wellbeing and can interact with treatments.

DIRECT TUMOUR EFFECTS

In most cases these are the signs for which attention for the patient is sought. In many cases a lump is found that might be ulcerated or bleeding. In some cases the signs are specific for an organ system, but neoplasia might not be evident on initial examination. This can be seen in patients with disease of the nervous system or gastrointestinal tract. If a mass is found then the best means of alleviating the signs is to remove the lump or treating it in other ways to reduce its size or release of cytokines if surgery is not possible. If there are severe signs associated with the mass then surgery may be indicated as a palliative measure, even if other therapies will be used as surgery is known not to be curative. An example of this is intestinal lymphoma which is generally treated with chemotherapy, but in cases with an obstructing mass I will offer surgery as the initial therapy.

These direct tumour effects can lead to problems. The owners want the mass removed immediately and do not want to wait a few days for pathology results from an aspirate or biopsy. Some will push to have the mass removed without any other staging or checks. This can compromise the long term outlook and make further treatment more difficult. In some cases the clients who push hard for this approach are also the clients who will complain the

most when things do not go as well as they might. Counselling the owners on the importance of a diagnosis, the possible outcomes and the complications that might arise if treatment is attempted without having all the information is very important.

ANAEMIA

Anaemia is a common finding in the cancer patient. All the types of anaemia can occur and neoplasia is a common underlying cause for immune mediated disease, in the few cases where a cause can be identified. In most cases the anaemia is relatively mild and is consistent with anaemia of chronic disease. This is usually of minor significance and has little impact on the patient or our treatments. It is only in the moderate to severe cases that treatment is needed as this can have more marked effects on the patient's wellbeing.

The first thing in any case with anaemia is to check if it is regenerative or not. In the latter cases we must remember that early in the course of regenerative causes of anaemia and in some immune mediated forms the evidence for regeneration may be lacking.

The signs of anaemia are well known: pallor, tachycardia, exercise intolerance, weakness and tachypnoea. But there can be general malaise and poor appetite which can be important in cancer patients. Wound healing can be impaired.

Blood loss anaemia

This is a relatively common form of anaemia in the cancer patient. It might be short term if the bleeding is internal, such as is seen with splenic or liver tumours. These patients may show the typical signs of anaemia and then proceed to recover over the course of the next few days, often in a repeating pattern. The anaemia is typically regenerative in the early stages, but in patients with external blood loss the development of iron deficiency can occur and then the anaemia can be non-regenerative as well as microcytic and hypochromic. With internal blood loss there can be red cell damage and schistocytes and other red cell fragments can be seen which overlaps with microangiopathic anaemia.

Blood loss anaemia is usually as a result of a bleeding tumour. Those of the intestinal and urinary tracts as well as some of the nasal tumours are the most common causes of external blood loss.

Any large internal tumour in the abdomen can cause internal bleeding. Mast cell tumours are the tumour that can cause indirect (usually intestinal) blood loss through histamine induced ulceration.

The ideal treatment is to remove the bleeding tumour. Blood transfusion may be needed prior to removal of the tumour. Iron supplementation might be needed in some cases of iron deficiency, but stopping the bleeding is usually sufficient.

Microangiopathic anaemia

This is usually seen in tumours that cause vascular plexuses such as haemangiosarcoma. The red cells are fragmented as they pass through the tumour by fibrin strands within the vascular beds and these damaged cells are then removed from the circulation with a shortened life span. This form of anaemia is often mild to moderate. If severe anaemia is seen there is often concurrent haemorrhage. While most often associated with vascular and splenic tumours, it can be seen with others including thyroid carcinomas and lymphoma.

Again the treatment is usually to remove the tumour with blood component support if needed. If the tumour is non-resectable and it is not known to be chemotherapy responsive, then the outlook is more guarded.

Immune mediated haemolytic anaemia

Most patients have an idiopathic disease, but in the patients where an underlying disease can be found, the most common is a lymphoproliferative disease, especially lymphoma. There is dysregulation of the immune system leading to loss of recognition of self antigens and haemolysis leading to a mild to severe anaemia.

Treatment is comprised of aggressively treating the underlying disease, immune suppression and blood transfusions if needed. In mild cases there is not a large influence on prognosis for the patient, but if severe there is a notable worsening of the prognosis.

Bone marrow disease

The bone marrow can be affected directly or indirectly. Anaemia of chronic disease is a form of indirect involvement. Most indirect forms are usually mild and of little significance in the management of the patient. Severe anaemia is seen most often as a result of bone marrow infiltration. Usually more than 75% of the bone marrow needs to be replaced by neoplastic cells before there is a notable decrease in red cell numbers but there can be suppression with lower levels of involvement. This amount of bone marrow involvement is generally only seen in lymphoma and leukaemias. Cats can have retroviral associated aplastic anaemia concurrent with a tumour. The latter usually have a very poor prognosis.

Treatment is generally targeted at the disease with some care taken to avoid drugs that are bone marrow suppressive. In most cases this is not possible and bone marrow suppressive drugs may need to be used in combination with transfusions and other supportive care.

HYPERCALCAEMIA

Neoplasia is the most common cause of clinically significant hypercalcaemia. This is seen more often in the dog than in the cat. In most patients that present with a calcium of > 4.0 mmol/l we usually have one of three diseases; lymphoma, anal sac carcinoma or primary hyperparathyroidism. There are a multitude of other potential causes the degree of hypercalcaemia is usually less or there are other marked changes to indicate the cause.

The main mechanisms of hypercalcaemia include increased levels of parathyroid hormone, elevated levels of parathyroid hormone related peptide, altered vitamin D metabolism and increased bone turnover or combinations of these.

Hypercalcaemia is an oncological emergency, mainly through the damage that can occur to the kidneys. The degree and duration of the hypercalcaemia does not predict the likelihood of renal failure. There is also no good indicators of the reversibility of the condition, though the more severe the azotaemia and hyperphosphataemia the lower the chances are that the condition can be reversed. In dogs with primary hyperparathyroidism the incidence of renal failure is lower than for other causes. The reason for this has not been elucidated.

If a patient is presented with hypercalcaemia this treatment must be started when it is first recognised. Intravenous saline diuresis is the mainstay of treatment, but any fluid will drop the calcium levels if saline is not available. If fluid therapy does not control the hypercalcaemia, then frusemide can be added in patients once they are hydrated. Glucocorticoids should only be used in cases that have been fully diagnosed and staged this can make getting a diagnosis more difficult and alter staging, especially for lymphoid tumours.

Long term treatment is based on controlling the underlying disease. In diseases such as anal sac carcinoma it can be used as an early sign of relapse or progression of metastatic disease. If the underlying diseases cannot be adequately treated then long term use of frusemide, glucocorticoids and bisphosphonates can be used. The latter drugs interfere with osteoclast activity and are moderately successful. In Australia the most readily available is the oral form alendronate sodium (Fosamax) which has no established dose rate but is usually started at 5 to 10mg SID per dog with a slow increase with tolerance and calcium levels. Gastrointestinal irritation is the most common toxicity seen with this drug.

HYPOGLYCAEMIA

This is seen most often with insulinoma and the classic signs are weakness and seizures. Other tumours can be associated with clinically significant hypoglycaemia and these include hepatic tumours, leiomyosarcomas and leiomyomas. There are isolated reports of many other tumours causing hypoglycaemia. In tumours other than insulinoma insulin levels are low and the hypoglycaemia is caused by a number of factors, most often insulin-like growth factor beta. There can be mild hypoglycaemia with any large tumour such as advanced lymphoma through increased utilisation, but this is generally not severe enough to cause any clinical signs.

Treatment is as usual best achieved through removal of the tumour. In cases where this is not possible some can be managed with frequent feedings and prednisolone can be used to cause insulin resistance in cases where insulin levels are increased. Diazoxide is useful in dogs with insulinoma and can control the signs for prolonged periods of time but is not available commercially in Australia. Streptozocin is a chemotherapy agent that is relatively specific for islet cells and has been used for insulinoma but is relatively poorly tolerated and is nephrotoxic. One study showed no survival benefit in patients treated with streptozocin over those treated with medical management alone.

For immediate treatment glucose infusions can be used. Other than in animals with seizures or severe signs, this is not recommended. In the insulinomas the glucose bolus can lead to an increase in insulin secretion and a rebound more severe hypoglycaemia.

VOMITING AND DIARRHOEA

This is more of a problem in patients after treatment but can be seen with tumours directly involving the gastrointestinal tract. Cases of mast cell tumour and lymphoma can have gastrointestinal signs without direct involvement. Chemotherapy is the treatment most often associated with these signs but radiation of the head and neck area can lead to signs in some patients.

Treatment is symptomatic. Fluid therapy should be considered in all cases. In patients with chemotherapy induced gastrointestinal signs I recommend that fluids be utilised early. Early intervention with support seems to reduce the time for recovery. I feel that it is better to give fluids to a patient who might have coped without them than to not give them to the patient who needed them. Anti-emetics should be used if vomiting is persistent. Metoclopramide given as an intermittent treatment or a CRI is often effective. In cases that are not responsive then maripitant or the 5HT3 antagonists dolasetron or ondansetron can be used. These are more effective, especially for chemotherapy induced vomiting, but are more expensive. I generally use them when metoclopramide has not been helpful or if the signs are severe.

Other treatments can be used on an as needed basis. H2 antagonists or omeprazole are useful for mast cell tumours. For most other cases the antacids and other gastric protectants are of little value. If blood is present then broad spectrum antibiotics (Amoxil and enrofloxacin combination or similar spectrum combination) should be used. For less severe cases there is some evidence that trimethoprim-sulphonamide combination has fewer disturbances to the normal intestinal flora and should be considered. In patients with signs of colitis I will generally add metronidazole.

NEUTROPENIA

A common toxicity of chemotherapy is neutropenia and it can be seen in patients with bone marrow disease and occasionally as an immune mediated disease. If present at severe levels, antibiotic coverage should be considered. I will always give broad spectrum coverage to patients with a fever or a neutrophil count that is less

than $0.5 \times 10^9/l$. I will consider it for patients with counts between 0.5 and $1.0 \times 10^9/l$ and use is dependent on the presence or absence of clinical signs. Unless there are gastrointestinal signs or fever I do not routinely give antibiotics to dogs with white cell counts greater than $1.0 \times 10^9/l$. Some drugs will cause more problems than others and this will alter the choice. I will use antibiotics more frequently in a patient who develops neutropenia secondary to doxorubicin than if they had received a drug such as CCNU. Some of this choice is based on the likelihood that they will develop concurrent gastrointestinal changes.

PAIN

This is not all that common except in cases with primary or secondary bone involvement. Some dogs and cats with visceral disease can be painful though distension especially of hollow organs. If the lesion can be removed, this is the most effective treatment.

For bone lesions that are not able to be removed the next best treatment has been course fraction radiation therapy with a 75% control of local pain for a period of months. This treatment can be repeated if needed. Non-steroidal anti-inflammatory drugs by themselves are poorly effective. Bisphosphonates (parental better than oral) in combination with a non-steroidal anti-inflammatory drug have shown some benefit and this appear to be further enhanced with the addition of chemotherapy. For severe and acute pain narcotics are the most effective especially if given as a CRI. These have problems with long term use due to tolerance developing and ceiling effects. Some long term patients can be managed with other drugs mentioned most of the time and narcotics used intermittently.

WEIGHT LOSS

Cancer cachexia is a problem in the cancer patient. Weight loss due to the effects of the tumour, poor appetite and pain the patient is less able to tolerate treatments and their quality of life is notably reduced. There is an increased risk of toxicities and reduced wound healing.

Getting food into the patient is the key. Eliminating all the factors that are contributing to poor appetite such as pain, fever, oral lesions, nausea, vomiting, diarrhoea etc is the first aim. Allowing access to foods and providing nutritious and calorie dense foods is

helpful. In some cases where a period of anorexia can be anticipated such as with oral surgery or radiation, then placing a feeding tube (preferably a gastrostomy tube) at the time of surgery allows easy access for feeding if needed and also provides an alternate means of giving medications in a patient likely to have a sore mouth. It is better to place a tube that is not used than to wait for problems to arise.

Long term diet therapy has been clearly shown to have a benefit in patients with lymphoma, but the metabolic derangements that are the basis of a diet such as Hill's n/d are present in many tumours and so there is possible benefit for any patient with a neoplasia. Studies have not been performed to date on patients with other tumours. The main problem with Hill's n/d is diarrhoea and this is seen mainly in patients who are not gradually introduced to the food.

HYPERTROPHIC OSTEOPATHY

This is a painful condition that arises in the distal limbs with mass lesions, usually in the thorax, but also with abdominal lesions. The distal limbs are warm, slightly swollen and painful. Radiographs show palisading of new bone under the periosteum of the distal bones. The cause is unknown. Treatment is removal of the underlying disease where possible and non-steroidal anti-inflammatory drugs or narcotics.

HYPERGLOBULINAEMIA

This is seen most often with plasma cell tumours but can be seen with lymphoma. Hyperviscosity syndrome (bleeding especially nasal, GI upsets, seizures, weakness, etc) can be seen. Treatment is control of the underlying disease. For severe acute disease then plasmapheresis is the treatment of choice, but this is not readily available anywhere in the world.

PALLIATION OF THE CANCER PATIENT

This is a combination of some or all of the above. There are patients for whom we do not have a lot to offer in the way of definitive treatments. There are others where for personal or financial reasons definitive treatment is not an option. In these

cases we should offer palliation as an option. Euthanasia is the most definitive form of palliation and is always an option.

I have seen some patients live for many months to years with disseminated tumours where we have been able to control the signs of the disease control pain and ensure adequate nutrition.

The main concern is that the owner is aware of our limitations. We must not keep a patient who is suffering alive because the owner cannot make the decision to treat aggressively or euthanase. It is our responsibility as veterinarians to keep the welfare of the patient as our primary concern. I have had some patients who the owners have not been able to make a decision to euthanase and I have told them that we can continue but only with the patient in a 24 hour care facility on a morphine infusion. I will increase the morphine to keep the patient comfortable with the owners aware that this action might lead to the death (but a comfortable one) of the patient. This is usually not an ideal situation for either the pet or the owners.

There are some patients who have malignant effusions. In these cases the signs often relate to the fluid, not the tumour. Removal of the fluid will improve the signs but it can often reform quickly. The use of intracavitary chemotherapy, usually cisplatin in the dog, can lead to long term control of the effusion and allow time for either other treatments to be used or sole palliation therapy. Likewise for dogs with pericardial effusion secondary to tumours of the heart base it has been shown that there can be long (18 month median) survival with a pericardiectomy as a sole therapy.

For patients who are well then nothing might need to be done at that time, but the owners should be counselled for the signs to watch for as indicators of problems. For many patients with carcinomas or sarcomas the use of a non-steroidal anti-inflammatory drug might help in several ways. There can be control of low grade discomfort we might be unable to detect. These drugs, particularly piroxicam, have been shown to slow progression of some tumours, primarily through inhibition of angiogenesis, but also with effects on the immune system and increasing apoptosis. If the tumours cannot form new blood vessels then they cannot grow. This can then lead to more quality time for the patient and owner. For lymphoproliferative diseases and leukaemias glucocorticoids can often be palliative. These cells release cytokines that make the patients feel unwell (flu like signs in people) and these can be suppressed by prednisolone. There can be some control of the underlying disease as well. Mast cell tumours can benefit from combination of antihistamines (both H1 and H2 antagonists), omeprazole as well as anti-inflammatory

doses of prednisolone. In all of these cases the treatment is aimed at not only buying time, but improving their quality of life.

Every case is different and every owner's wishes and desires also vary. We cannot cater for everyone, but we should strive to give every owner all the options. There is always a treatment option for a patient with cancer.

FUTURE TRENDS

With time new drugs will be developed that will reduce nausea and vomiting. But the overall effects of the drugs will not greatly alter. What has been seen in recent years is the increasing use of prophylactic supportive care. As narcotics work best when given prior to the development of a painful lesion, so the use of pre-emptive treatments for gastrointestinal signs and fever works better than trying to treat them once the signs have developed. The early use of fluids and other supportive measures has improved the quality of life of many patients. This has led to less treatment delays, intensification of protocols without a reduction in quality of life for the patients.

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